Synthesis of bridged azabicycles from isoquinolines *via* a tandem of allylboration and intramolecular metathesis*

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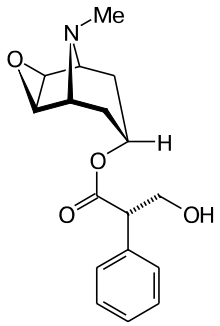
A method for the synthesis of bridged azabicyclic compounds from isoquinolines was developed. The method is based on a combination of allylboration and ruthenium-catalyzed intramolecular metathesis. Reductive 1,3-diallylation of bromoisoquinolines with triallylborane gave *trans*-1,3-diallyl-1,2,3,4-tetrahydroisoquinolines. When heated with triallylborane, these compounds yielded mixtures of *cis*- and *trans*-isomers in the ratio ~1 : 1. The structure of *cis*-1,3-diallyl-5-bromo-1,2,3,4-tetrahydroisoquinoline was confirmed by X-ray diffraction analysis. In a similar way, *trans*-3-allyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline synthesized by sequential vinylation (with vinyllithium) and allylboration of isoquinoline, yielded a mixture of *cis*- *and trans*-isomers in the ratio 1.6 : 1. Intramolecular metathesis reactions of *N*-Boc derivatives of *cis*-isomers in the presence of the Grubbs catalyst (2.0—2.5 mol.%) afforded 7,8-benzo-10-azabicyclo[4.3.1]dec-2-enes or 7,8-benzo-9-azabicyclo[3.3.1]non-2-ene in nearly quantitative yields.

Key words: triallylborane, allylboranes, allylboronation, nitrogen-containing heterocycles, cyclization, isoquinolines, metathesis.

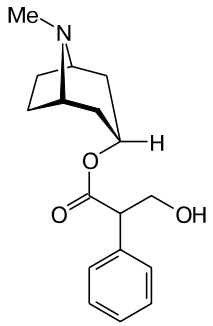
Bridged azabicyclic compounds are a unique class of compounds that exhibit a broad spectrum of biological activity[1] in spite of their simple structures. It should be noted that some of them (*e.g.*, atropine, scopolamine, and cocaine) have long been used in folk medicine and at present they are employed in official medicine;[1c] (+)-ferruginine and (+)-anatoxin-*a*, which are highly neuroactive, are considered to be potential candidates for treating the Alzheimer disease.[1d] That is why development of efficient methods for construction of azabicyclic structures is of current interest in modern synthetic organic chemistry.

Although intramolecular metathesis has long become an efficient tool in the design of cyclic systems,[2] its use for the formation of a bicyclic structure in the synthesis of bridged azabicycles has been reported only in few papers.[3] This is due to inaccessibility of substrates suitable for the metathesis reaction. Nevertheless, the results obtained clearly show a high potential of the metathesis reaction in the synthesis of bridged azabicyclic systems.

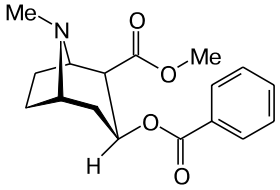
Recently,[4] we have proposed a simple and efficient strategy for design of 9-azabicyclo[4.2.1]nonenes and a number of 10-azabicyclo[4.3.1]decadienes. The strategy involves a tandem of diallylboration of aromatic hetero-



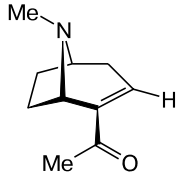
Scopolamine



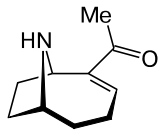
Atropine



Cocaine



(+)-Ferruginine



(+)-Anatoxin-*a*

* Dedicated to Academician V. A. Tartakovsky on the occasion of his 75th birthday.

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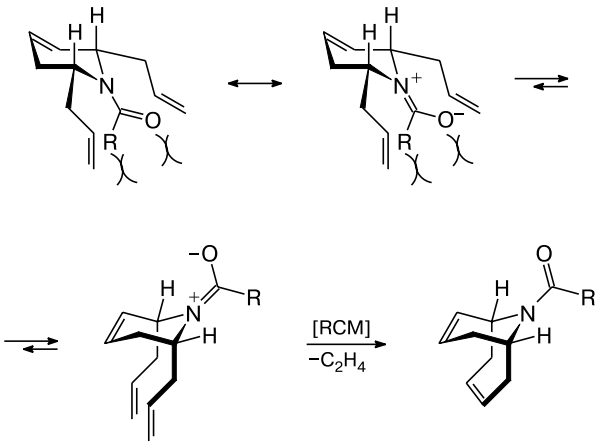
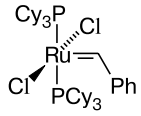
cycles (pyridines and pyrrole) and intramolecular metathesis. We have used *N*-Boc-protected α,α′-diallylated heterocycles with *cis*-arrangement of the allyl groups as the starting reagents (Scheme 1). The presence of acyl protection is indispensable for the metathesis reaction: first, acylation suppresses the basic properties of the amino group[5] and, second, ensures the optimal conformation of the molecule with axially aligned substituents because of a 1,3-allylic strain.[6,3a]

Scheme 1



To extend the area of application of this method, we obtained two novel bromine-containing 7,8-benzo-10-azabicyclo[4.3.1]dec-2-enes from appropriate bromoisoquinolines and the 9-azabicyclo[3.3.1]non-2-ene system from isoquinoline. In the latter case, we used for the first time a combination of vinylation—allylboronation—metathesis catalyzed by the first generation Grubbs catalyst (**I**, Cy is cyclohexyl).



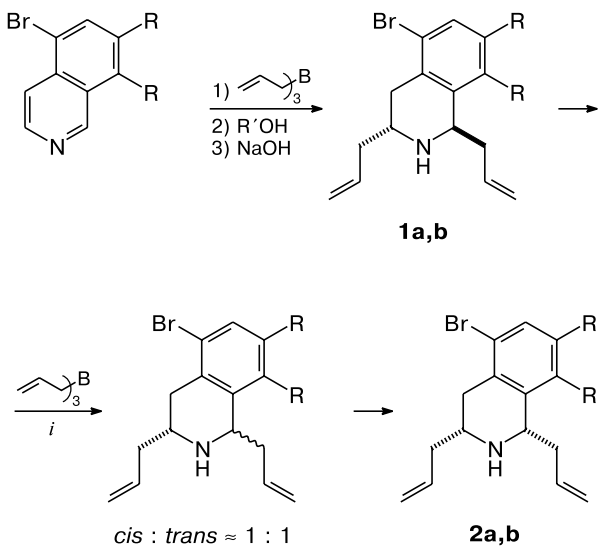
I

Results and Discussion

Reactions of triallylborane with bromoisoquinolines in the presence of alcohols gave *trans*-1,3-diallylbromo-1,2,3,4-tetrahydroisoquinolines[7] (**1a,b**) (Scheme 2). The mechanism of reductive diallylation of aromatic nitrogen heterocycles with allylboranes has been thoroughly examined earlier with pyridines as examples.[8]

Heating of *trans*-isomers **1a,b** with triallylborane (1 : 1) at 130—135 °C yielded a mixture of *cis*- (**2a,b**) and *trans*-isomers (**1a,b**) in the ratio ~1 : 1. This ratio remained unchanged with time and is probably an equilibrium one.[4] Isomerization involves protolytic cleavage of one B—C bond in triallylborane with liberation of propene followed by deallylboration—allylboration.[8] The corresponding *cis*-isomers **2a,b** were isolated by chromatography and the

Scheme 2



R = H (**a**), Br (**b**)

i. 130—135 °C, 2 h.

structure of compound **2a** was confirmed by X-ray diffraction analysis (Fig. 1). According to X-ray diffraction data, compound **2a** crystallizes as a racemate. The nitrogen-containing six-membered ring exists in the half-chair conformation; the N(2) and C(3) atoms deviate by 0.52 and 0.24 Å, respectively, from the plane formed by the C(1), C(8A), C(4A), and C(4) atoms. The N atom in compound **2a** has a pyramidal configuration (the sum of the bond angles is 328°). The allyl substituents are *cis* to each other and are in the equatorial and pseudoequatorial positions. The amino group is shielded by the allyl substituents, which probably prevents intermolecular N—H...Br interactions in the crystal.

Treatment of amines **2a,b** with Boc anhydride quantitatively gave Boc amides **3** (Scheme 3). In the presence of catalyst **I** in CH_2Cl_2, they underwent cyclization into bicyclic compounds **4a,b** in nearly quantitative yields.

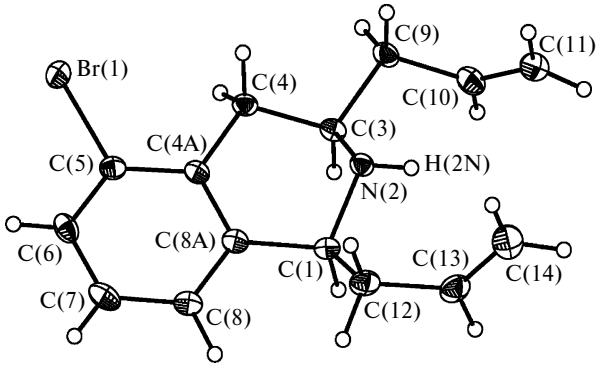
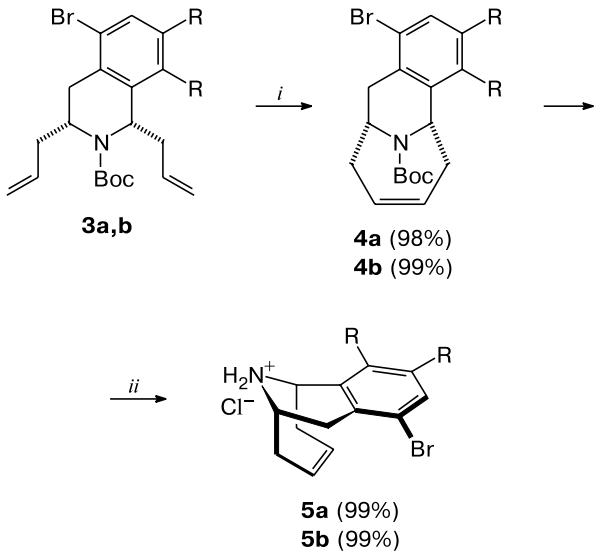


Fig. 1. General view of compound **2a**.

Scheme 3



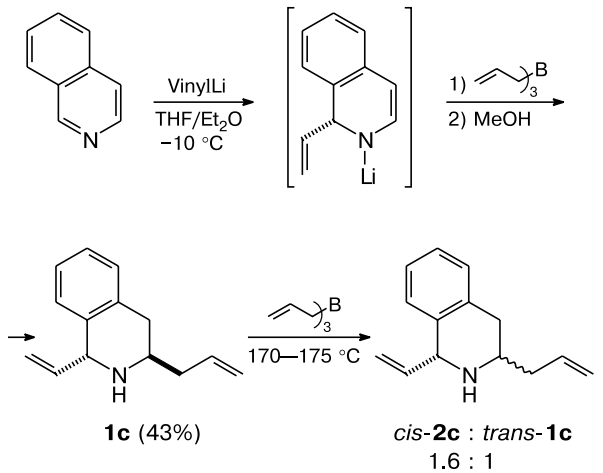
R = H (**a**), Br (**b**)

Reagents and conditions: *i*. **I**, CH_2Cl_2; *ii*. HCl, dioxane, 70 °C.

It should be noted that the NMR spectra of Boc derivatives **3** and **4** are poorly informative because of signal doubling and broadening due to hindered rotation about the amide bond. Elimination of the protective group from compounds **4a,b** by heating with HCl in dioxane gave hydrochlorides **5a,b** in quantitative yields. Compound **5b** is poorly soluble even in hot DMSO.

This method also affords bicyclic compounds with a contracted ring. For this purpose, we used our method for the synthesis of *trans*-1-alkyl- and *trans*-1-aryl-3-allyl-1,2,3,4-tetrahydroisoquinolines.[9] Treatment of isoquinoline with vinyllithium (prepared from vinyl bromide and *tert*-butyllithium)[10] led to lithium 1-vinylamide

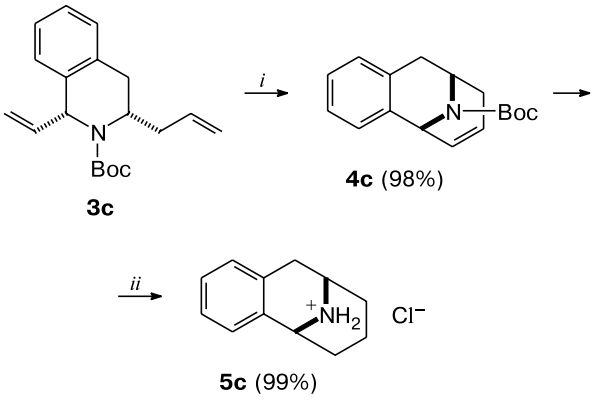
Scheme 4



(Scheme 4), which was successively treated *in situ* with triallylborane and methanol to give *trans*-3-allyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline (**1c**) in 43% yield.

Heating of *trans*-amine **1c** with triallylborane (1 : 1) at 170 °C for 9 h resulted in an equilibrium mixture of *cis*-**2c** and *trans*-**1c** in the ratio 1.6 : 1; the total yield was 90% with respect to the consumed *trans*-**1c** (see Scheme 4). Treatment of amine **2c** with Boc anhydride quantitatively gave amide **3c**; its cyclization in the presence of Grubbs catalyst **I** was much faster than the cyclization of diallyl derivatives[4] and was completed in 30 min (Scheme 5). Bicyclic amide **4c** was isolated by chromatography in 98% yield; its treatment with HCl gave hydrochloride **5c** in 99% yield.

Scheme 5



Reagents and conditions: *i*. **I**, CH_2Cl_2; *ii*. HCl, dioxane, 80 °C.

In conclusion, we developed a method for the synthesis of 7,8-benzo-9-azabicyclo[3.3.1]non-2-ene and bromo-7,8-benzo-10-azabicyclo[4.3.1]dec-2-enes *via* combination of allylboration and intramolecular metathesis in the presence of the Grubbs ruthenium catalyst. To obtain the 9-azabicyclo[3.3.1]non-2-ene system, we employed for the first time the vinylation—allylboration—metathesis combination.

Experimental

Reactions were carried out under dry argon. All solvents were purified according to standard procedures. NMR spectra were recorded on Bruker Avance-300, Bruker Avance-400, and Bruker Avance-600 spectrometers. Column chromatography was carried out on silica gel (60—230 mesh, Merck). Bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (**I**) (Aldrich) was used as a catalyst. Compounds **1a,b** were prepared as described earlier[7a] (except that benzene as a solvent was replaced by CH_2Cl_2). 5-Bromoisoquinoline was prepared from a 5-amino derivative as described earlier.[7b]

***trans*-1,3-Diallyl-5-bromo-1,2,3,4-tetrahydroisoquinoline (1a).** Triallylborane (5.2 mL, 4 g, 30 mmol) was added at −30 °C

to a stirred solution of 5-bromoisoquinoline (5 g, 24 mmol) in CH_2Cl_2 (10 mL). The mixture was gradually warmed to 0 °C. Then methanol (3.8 g, 4.9 mL, 0.12 mol) was added in two portions, which resulted in self-heating to boiling. The mixture was refluxed for 1.5 h and then concentrated under reduced pressure. A 20% solution of NaOH (10 mL) was added to the residue and the mixture was refluxed for 1 h. On cooling, the product was extracted with ether (3×15 mL). The organic layer was separated, dried over K_2CO_3, and concentrated. The yield of compound **1a** was 7 g (99%), R_f 0.51 (hexane—EtOAc , 4 : 1). The product was sufficiently pure for use at the next step (^{1}H NMR data; *cf.* Ref. 7a).

***cis*-1,3-Diallyl-5-bromo-1,2,3,4-tetrahydroisoquinoline (2a).** Triallylborane (3.75 g, 4.85 mL, 28 mmol) was added to stirred and degassed *trans*-**1a** (6.7 g, 22.9 mmol). The reaction mixture spontaneously heated and propene evolved. After active evolution of the gas ceased, the mixture was heated on an oil bath at 130 °C for 2 h. On cooling to 20 °C, methanol (5 mL) was added. The resulting solution was refluxed for 1 h and then treated with 20% NaOH (10 mL). The product was extracted with toluene (3×15 mL). The organic extract was dried over K_2CO_3 and concentrated in a rotary evaporator. The residue was chromatographed on silica gel with *n*-hexane—EtOAc (6 : 1) as an eluent. The yield of *cis*-**2a** was 3.31 g (49%), R_f 0.47, transparent orange crystals, m.p. 64.5—65.5 °C (*n*-hexane). The starting compound *trans*-**1a** (3.12 g) was recovered, R_f 0.30. Found (%): C, 61.67; H, 6.23; N, 4.78; Br, 27.40. $C_{15}H_{18}BrN$. Calculated (%): C, 61.65; H, 6.21; N, 4.79; Br, 27.34. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.45 (d, 1 H, C(6)H, J = 7.9 Hz); 7.33 (d, 1 H, C(8)H, J = 7.9 Hz); 7.12 (t, 1 H, C(7)H, J = 7.9 Hz); 5.98—5.75 (m, 2 H, 2 CH=); 5.20—5.04 (m, 4 H, 2 CH_2=); 4.06 (dm, 1 H, C(1)H, J = 4.4 Hz); 2.89—2.73 (m, 3 H, C(3)H, C(4)H_2); 2.46—2.36 (m, 1 H, C(9)$\underline{H}_aH_b$); 2.36—2.24 (m, 4 H, C(9)$H_a\underline{H}_b$, C(12)H_2 + 1 NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 141.13 (C); 135.40 (C); 134.83 (2 CH=$_{all}$ coalescence of two peaks); 130.23 (C(6)H_{arom}); 126.96 (C(7)H_{arom}); 125.75 (CBr); 124.07 (C(8)H_{arom}); 118.62, 118.04 (2 CH_2=$_{all}$); 55.98 (C(1)NH); 52.45 (C(3)NH); 40.96 (CH_2); 40.16 (CH_2); 37.51 (CH_2).

***cis*-1,3-Diallyl-5,7,8-tribromo-1,2,3,4-tetrahydroisoquinoline (2b)** was obtained analogously from *trans*-**1a** (4.26 g, 9.5 mmol) (see Ref. 7a) and triallylborane (1.52 g, 11.3 mmol). According to the ^{1}H NMR spectrum, the *trans*-**2b**/*cis*-**2b** ratio is 1.16 : 1. The products were isolated by chromatography on silica gel with *n*-hexane—EtOAc (11 : 1) as an eluent. The fractions with R_f 0.33 (**1b**, crystals) and 0.28 (**2b**, an oil) were collected. The yield of *cis*-**2b** was 1.91 g (45%). Found (%): C, 40.05; H, 3.61; N, 3.11; Br, 53.41. $C_{15}H_{16}Br_3N$. Calculated (%): C, 40.04; H, 3.58; N, 3.11; Br, 53.27. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.70 (s, 1 H, CH_{arom}); 5.87—5.77 (m, 1 H, CH=$_{all}$); 5.68—5.58 (m, 1 H, CH=$_{all}$); 5.16—5.04 (m, 4 H, 2 CH_2=$_{all}$); 4.46 (d, 1 H, C$\underline{H}$NAr, J = 5.4 Hz); 2.86 (d, 1 H, C$\underline{H}_aH_b$Ar, J = 16.5 Hz); 2.70—2.62 (m, 2 H, $CH_{2(all)}$); 2.46—2.38 (m, 1 H, C$\underline{H}$N); 2.34—2.24 (m, 2 H, $CH_{2(all)}$); 2.20 (dd, 1 H, $CH_a\underline{H}_b$Ar, J = 11.2 Hz, J = 16.0 Hz); 1.48 (br.s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 143.01; 137.90; 134.58; 134.53; 133.85; 124.37; 123.84; 121.75; 118.40; 117.96; 57.91; 51.68; 40.95; 40.76; 37.27.

***N*-*tert*-Butoxycarbonyl-7,8-(5′-bromobenzo)-10-azabicyclo[4.3.1]dec-3-ene (4a).** A solution of compound **2a** (0.58 g, 2.0 mmol) and Boc anhydride (0.46 g, 2.1 mmol) in THF (5 mL) was refluxed until the starting amine was completely consumed (~1 h). The course of the reaction was monitored by TLC (*n*-hexane—EtOAc, 6 : 1). The solvent was removed under reduced pressure and the residue was dried *in vacuo* and used without additional purification. The yield of compound **3a** was 0.77 g (98%), an oil. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.47 (dd, 1 H_{arom}, J = 1.0 Hz, J = 7.9 Hz); 7.21 (br.d, 1 H_{arom}, J = 7.4 Hz); 7.09 (t, 1 H_{arom}, J = 7.8 Hz); 5.86—5.76 (m, 2 H, 2 CH=$_{all}$); 5.18—4.99 (br.m, 5 H, 2 CH_2=$_{all}$, C$\underline{H}$NAr); 4.26—3.90 (br.m, 1 H, C$\underline{H}_aH_b$Ar); 3.18—2.91 (br.s, 1 H, $CH_a\underline{H}_b$Ar); 2.80 (dd, 1 H, C$\underline{H}_aH_{b(all)}$, J = 7.7 Hz, J = 16.5 Hz); 2.54—2.42 (br.m, 3 H, $CH_{2(all)}$, C$\underline{H}$N); 2.30—2.21 (m, 1 H, $CH_a\underline{H}_{b(all)}$); 1.37 (s, 9 H, Bu^t).

The solution of compound **3a** (0.40 g, 1.0 mmol) in CH_2Cl_2 (7 mL) was degassed and catalyst **I** (21 mg, 2.5 mol.%, 0.026 mmol) was added. The course of the reaction was monitored by TLC (*n*-hexane—EtOAc (9 : 1), R_f(**3a**) 0.65; R_f(**4a**) 0.54). The reaction mixture was heated at 40 °C for 1.5 h until the starting compound **3a** was completely consumed. The solvent was removed, hexane (15 mL) and EtOAc (1 mL) were added, and the solution was filtered and concentrated. The residue was chromatographed on silica gel with *n*-hexane—EtOAc (11 : 1) as an eluent. The yield of product **4a** was 0.36 g (98%), crystals, m.p. 131—132 °C (*n*-hexane). Found (%): C, 59.38; H, 6.12; N, 3.78. $C_{18}H_{22}BrNO_2$. Calculated (%): C, 59.35; H, 6.09; N, 3.85. ^{1}H NMR (400 MHz, DMSO-d_6), δ*: 7.36 (d, 1 H_{arom}, J = 5.8 Hz); 7.13 (two doublets, in total 1 H_{arom}); 7.02 (two triplets, in total 1 H_{arom}); 5.65—5.60 (m, 1 H, CH=); 5.33—5.23 (m, 2 H, CH=, CHNAr); 4.70—4.61 (m, 1 H, CHN); 2.89—2.81 (m, 1 H, C$\underline{H}_aH_b$Ar); 2.63—2.57 (m, 2 H, C$\underline{H}_2$CH=); 2.53—2.49 (m, 1 H, $CH_a\underline{H}_b$Ar); 2.39 (br.d, J = 11.6 Hz, 1 H, C$\underline{H}_aH_b$CH=); 2.30—2.18 (m, 1 H, $CH_a\underline{H}_b$CH=); 1.42, 1.41 (both s, in total 9 H, Bu^t).

***N*-*tert*-Butoxycarbonyl-7,8-(5′,7′,8′-tribromobenzo)-10-azabicyclo[4.3.1]dec-3-ene (4b)** was obtained analogously. Boc derivative **3b** was prepared from compound **2b** (0.7 g, 1.6 mmol) and Boc anhydride (0.36 g, 1.64 mmol). The yield of compound **3b** was 0.87 g (99%), an oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.83 (s, 1 H_{arom}); 6.03—5.86 (br.m, 3 H, 2 CH=$_{all}$, CHNAr); 5.27—5.15 (m, 4 H, 2 CH_2=$_{all}$); 4.03—3.91 (br.m, 1 H, CHN); 3.51 (dd, 1 H, C$\underline{H}_aH_b$Ar, J = 7.3 Hz, J = 16.6 Hz); 2.97—2.89 (br.m, 1 H, C$\underline{H}_aH_{b(all)}$); 2.65 (dd, 1 H, $CH_a\underline{H}_b$Ar, J = 11.3 Hz, J = 16.6 Hz); 2.47—2.32 (m, 3 H, $CH_a\underline{H}_{b(all)}$, $CH_{2(all)}$); 1.52 (s, 9 H, Bu^t).

Cyclization of compound **3b** (0.83 g, 1.5 mmol) was carried out in the presence of catalyst **I** (2.5 mol.%, 31 mg, 0.04 mmol) in CH_2Cl_2 (8 mL). The yield of product **4b** was 0.76 g (98%), large crystals, m.p. 125—126 °C (*n*-hexane). Found (%): C, 41.39; H, 3.85; N, 2.70. $C_{18}H_{20}Br_3NO_2$. Calculated (%): C, 41.41; H, 3.86; N, 2.68. ^{1}H NMR (300 MHz, $CDCl_3$), δ*: 7.86 (s, 1 H_{arom}); 5.84, 5.73 (br.s, in total 2 H, 2 CH=); 5.49 (br.s, 1 H, CHNAr); 4.90, 4.76 (br.m, in total 1 H, CHN); 2.98 (dd, 2 H, C$\underline{H}_aH_b$Ar, C$\underline{H}_aH_b$CH=, J = 8.9 Hz, J = 18.0 Hz); 2.70 (d, 1 H, $CH_a\underline{H}_b$Ar, J = 18.1 Hz); 2.77—2.56 (m, 2 H, C$\underline{H}_2$CH=); 2.38, 2.33 (dd, in total 1 H, $CH_a\underline{H}_b$CH=, J = 5.5 Hz, J = 8.1 Hz), 1.58, 1.56 (br.s, in total 9 H, Bu^t).

7,8-(5′-Bromobenzo)-10-azabicyclo[4.3.1]dec-3-ene hydrochloride (5a). A 5.3 *M* solution of HCl (0.38 mL, 2.0 mmol) in

* The signals in the NMR spectrum are broadened and doubled because of hindered rotation in the amide fragment.

dioxane was added to a solution of compound **4a** (0.18 g, 0.49 mmol) in dioxane (0.7 mL). The resulting solution was heated at 70 °C for 40 min until the starting compound **4a** was completely consumed (monitoring by TLC). Then Et_2O (5 mL) was added and the precipitate was filtered off and dried *in vacuo*. The yield of product **5a** was 0.14 g (99%), white crystals, m.p. 251—252 °C. Found (%): C, 51.98; H, 5.09; N, 4.60. $C_{13}H_{15}BrClN$. Calculated (%): C, 51.94; H, 5.03; N, 4.66. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 10.57, 10.26 (both br.s, 1 H each, NH_2^+); 7.58 (d, 1 H_{arom}, J = 7.9 Hz); 7.34 (d, 1 H_{arom}, J = 7.5 Hz); 7.21 (dd, 1 H_{arom}, J = 7.9 Hz, J = 7.6 Hz); 5.76 (m, 1 H, CH=); 5.34 (m, 1 H, CH=); 4.88 (m, 1 H, CHNAr); 4.08 (m, 1 H, CHN); 3.15—3.06 (m, 2 H, C$\underline{H}_a$$H_bAr, C\underline{H}_a$$H_b$CH=); 2.93 (d, 1 H, C$H_a\underline{H}_b$CH=, J = 16.4 Hz); 2.76—2.67 (m, 2 H, C$H_a\underline{H}_b$Ar, C$\underline{H}_a$·H_b·CH=); 2.61 (dd, 1 H, CH_a·$\underline{H}_b$·CH=, J = 4.8 Hz, J = 8.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 135.26 (s); 132.32 (s); 131.74; 129.77; 129.47; 128.37; 126.22; 124.24 (s); 49.39 (CH); 45.51 (CH); 33.19; 31.99; 31.31.

7,8-(5′,7′,8′-Tribromobenzo)-10-azabicyclo[4.3.1]dec-3-ene hydrochloride (5b) was obtained analogously from compound **4b** (0.54 g, 1.0 mmol). The yield was 0.47 g (99%), small cream-colored crystals, m.p. 326—327 °C. Found (%): C, 34.01; H, 2.87; N, 3.05. $C_{13}H_{13}Br_3ClN$. Calculated (%): C, 34.06; H, 2.86; N, 3.06. ^{1}H NMR (600 MHz, DMSO-d_6), δ: 10.24 (br.s, 2 H, NH_2^+); 8.11 (s, 1 H_{arom}); 5.79 (m, 1 H, CH=); 5.39 (m, 1 H, CH=); 4.93 (dd, 1 H, CHNAr, J = 2.9 Hz, J = 4.6 Hz); 4.07 (m, 1 H, CHN); 3.02 (dd, 1 H, C$\underline{H}_a$$H_b$Ar, J = 8.9 Hz, J = 18.7 Hz); 2.99—2.94 (m, 2 H, C$\underline{H}_a$$H_b$CH=, C$\underline{H}_a$·$H_b$·CH=); 2.85 (d, 1 H, C$H_a\underline{H}_b$CH=, J = 17.2 Hz); 2.67 (d, 1 H, C$H_a\underline{H}_b$Ar, J = 18.7 Hz); 2.58 (ddd, 1 H, CH_a·$\underline{H}_b$·CH=, J = 5.3 Hz, J = 8.2 Hz, J = 16.3 Hz). ^{13}C NMR (150 MHz, DMSO-d_6), δ: 135.81; 135.75; 134.92; 130.23; 129.56; 124.41; 124.21; 123.31; 51.04; 45.30; 32.02; 31.52; 28.85.

***trans*-3-Allyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline (1c).** A solution of isoquinoline (2.0 g, 15.5 mmol) in Et_2O (4 mL) was added at −10 °C to a solution of vinyllithium (prepared from vinyl bromide (18 mmol) and Bu^tLi (36 mmol))[10] in Et_2O (15 mL). The reaction mixture was stirred at −5 to 0 °C for 2 h and then cooled to −15 °C. Triallylborane (2.4 g, 3.1 mL, 18 mmol) was added with stirring. After 15 min, MeOH (10 mL) was added and stirring was continued at 20 °C for an additional 20 min. The reaction mixture was decomposed with 6 *N* HCl (3 mL, 18 mmol) and then (after 30 min) with 20% NaOH (10 mL, 60 mmol). The organic layer was separated, washed with brine, dried over K_2CO_3, and concentrated under reduced pressure. The residue was chromatographed on silica gel with *n*-hexane—EtOAc (5 : 1) as an eluent, R_f 0.28. The yield of compound **1c** was 1.34 g (43%), a yellow oil. Found (%): C, 84.28; H, 8.75; N, 7.08. $C_{14}H_{17}N$. Calculated (%): C, 84.37; H, 8.60; N, 7.03. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.14—7.09 (m, 4 H_{arom}); 6.11 (ddd, 1 H, $CH=_{vinyl}$, J = 6.8 Hz, J = 10.0 Hz, J = 17.0 Hz); 5.92—5.82 (m, 1 H, $CH=_{all}$); 5.22—5.13 (m, 3 H, $CH_2=_{all}$, C$\underline{H}_a$$H_b$$=_{vinyl}$); 5.08 (d, 1 H, C$H_a\underline{H}_b$$=_{vinyl}$, J = 17.0 Hz); 4.60 (d, 1 H, CNHAr, J = 6.8 Hz); 3.22—3.16 (m, 1 H, CHN); 2.80 (dd, 1 H, C$\underline{H}_a$$H_b$Ar, J = 3.8 Hz, J = 16.3 Hz); 2.59 (dd, 1 H, C$H_a\underline{H}_b$Ar, J = 10.0 Hz, J = 16.3 Hz); 2.38—2.31 (m, 1 H, C$\underline{H}_a$$H_{b(all)}$); 2.27—2.20 (m, 1 H, C$H_a\underline{H}_{b(all)}$); 1.88 (br.s, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 141.19; 136.06; 135.15; 134.80; 129.19; 128.02; 126.40; 125.60; 117.71; 115.40; 58.62; 47.13; 40.82; 35.58.

***cis*-3-Allyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline (2c).** Compound **1c** (1.28 g, 6.4 mmol) was mixed with triallylborane (0.95 g, 1.22 mL, 7.0 mmol). The mixture was heated at 170—175 °C for 9 h. On cooling, the mixture was decomposed with MeOH (2 mL) and, after gas evolution ceased, with 20% NaOH (3 mL). The mixture was refluxed for 30 min. The product was extracted with ether—hexane (3×5 mL). The combined extracts were dried over K_2CO_3 and concentrated under reduced pressure. The *cis*/*trans* ratio was 1.62 : 1 (^{1}H NMR data). The yield of a mixture of compounds **1c** and **2c** was 1.15 g (90%), an oil. The residue was purified by chromatography on silica gel with *n*-hexane—EtOAc (5 : 1) as an eluent, R_f(**2c**) 0.47. The yield of compound **2c** was 0.7 g. Found (%): C, 84.28; H, 8.75; N, 7.08. $C_{14}H_{17}N$. Calculated (%): C, 84.24; H, 8.72; N, 6.97. ^{1}H NMR (600 MHz, $CDCl_3$), δ: 7.17 (br.s, 3 H_{arom}); 7.12—7.10 (m, 1 H_{arom}); 5.94—5.85 (m, 2 H, 2 CH=); 5.40 (d, 1 H, C$\underline{H}_a$$H_b$$=_{vinyl}$, J = 17.0 Hz); 5.33 (dd, 1 H, C$\underline{H}_a$$H_b$$=_{all}$, J = 1.4 Hz, J = 9.6 Hz); 5.24 (d, 1 H, C$H_a\underline{H}_b$$=_{vinyl}$, J = 16.9 Hz); 5.19 (d, 1 H, C$H_a\underline{H}_b$$=_{all}$, J = 10.1 Hz); 4.52 (d, 1 H, CHNAr, J = 8.7 Hz); 3.07—3.03 (m, 1 H, CHN); 2.78 (dd, 1 H, C$\underline{H}_a$$H_b$Ar, J = 3.6 Hz, J = 16.0 Hz); 2.71 (dd, 1 H, C$H_a\underline{H}_b$Ar, J = 11.0 Hz, J = 16.0 Hz); 2.44—2.40 (m, 1 H, C$\underline{H}_a$$H_{b(all)}$); 2.31—2.26 (m, 1 H, C$H_a\underline{H}_{b(all)}$); 2.10 (br.s, 1 H, NH). ^{13}C NMR (150 Hz, $CDCl_3$), δ: 140.48; 136.82 C; 134.98; 134.82 C; 129.04; 126.71; 126.47; 125.76; 118.01; 117.90; 62.39; 52.59; 41.25; 36.21.

***cis*-3-Allyl-2-*tert*-butoxycarbonyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline (3c).** Amine **2c** (0.47 g, 2.36 mmol) and Boc anhydride (0.55 g, 2.52 mmol) in THF (5 mL) was refluxed for 1 h. The course of the reaction was monitored by TLC (*n*-hexane—EtOAc, 5 : 1). The solvent was removed *in vacuo* and the residue was dissolved in *n*-hexane—EtOAc (9 : 1). The solution was passed through a short column of silica gel to remove trace amounts of the amine. The yield of compound **3c** was 0.68 g (97%), an oil. Found (%): C, 76.28; H, 8.35; N, 4.59. $C_{19}H_{25}NO_2$. Calculated (%): C, 76.22; H, 8.42; N, 4.68. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.25—7.21 (m, 3 H_{arom}); 7.19—7.14 (m, 1 H_{arom}); 6.00—5.79 (m, 2 H, 2 CH=); 5.58 (br.s, 1 H, CHNAr); 5.28—5.23 (m, 2 H, CH_2=); 5.12—5.04 (m, 2 H, CH_2=); 4.58 (br.s, 1 H, CHN); 3.02 (dd, 1 H, C$\underline{H}_a$$H_b$Ar, J = 6.1 Hz, J = 15.6 Hz); 2.84 (dd, 1 H, C$H_a\underline{H}_b$Ar, J = 4.2 Hz, J = 15.6 Hz); 2.46 (br.s, 1 H, C$\underline{H}_a$$H_{b(all)}$); 2.27—2.17 (m, 1 H, C$H_a\underline{H}_{b(all)}$); 1.55 (s, 9 H, Bu^t).

***N-tert*-Butoxycarbonyl-7,8-benzo-9-azabicyclo[3.3.1]non-2-ene (4c).** A solution of compound **3c** (0.36 g, 1 mmol) in CH_2Cl_2 (8 mL) was degassed. Catalyst **I** (2.0 mol.%, 16 mg, 0.02 mmol) was added and the mixture was stirred at 30 °C for 30 min. The course of the reaction was monitored by TLC (*n*-hexane—EtOAc, 10 : 1). The solvent was removed under reduced pressure and the residue was diluted with hexane and chromatographed on silica gel with *n*-hexane—EtOAc (10 : 1) as an eluent. The yield of compound **4c** was 0.32 g (98%), m.p. 73—74 °C. Found (%): C, 75.28; H, 7.85; N, 5.09. $C_{17}H_{21}NO_2$. Calculated (%): C, 75.25; H, 7.80; N, 5.16. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.17 (br.s, 4 H_{arom}); 5.96, 5.80 (both br.m, in total 2 H, 2 CH=); 5.49, 5.30 (both d, in total 1 H, CHNAr, J = 4.4 Hz, J = 5.3 Hz); 4.95, 4.84 (both m, in total 1 H, CHN); 3.54—3.45 (m, 1 H, C$\underline{H}_a$$H_b$CH=); 2.78—2.63 (m, 2 H, C$\underline{H}_2$Ar); 2.06—2.01 (m, 1 H, C$H_a\underline{H}_b$CH=); 1.50, 1.44 (both s, in total 9 H, Bu^t).

7,8-Benzo-9-azabicyclo[3.3.1]non-2-ene hydrochloride (5c). A 5.3 *M* solution of HCl (0.47 mL, 2.5 mmol) in dioxane was added to a solution of bicyclic compound **4c** (0.21 g, 0.8 mmol) in dioxane (1 mL). The mixture was heated at 80 °C for 30 min until the starting amide was completely consumed. The resulting suspension was diluted with Et_2O (5 mL) and the precipitate was filtered off and dried *in vacuo*. The yield of product **5c** was 0.15 g (99%), white crystals, m.p. 279—281 °C. Found (%): C, 69.39; H, 6.69; N, 6.69. $C_{12}H_{14}NCl$. Calculated (%): C, 69.39; H, 6.79; N, 6.74. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 10.25, 9.83 (both br.s, 1 H each, NH_2^+); 7.34—7.22 (m, 4 H_{arom}); 5.96—5.95 (m, 1 H, CH=); 5.85—5.82 (m, 1 H, CH=); 4.98 (d, 1 H, CHNAr, J = 4.8 Hz); 4.19—4.14 (m, 1 H, CHN); 3.56 (dd, 1 H, C$\underline{H}_a$H$_b$CH=, J = 8.9 Hz, J = 18.5 Hz); 2.90—2.81 (m, 1 H, C$\underline{H}_a$H$_b$Ar); 2.86 (d, 1 H, CH$_a\underline{H}_b$Ar, J = 18.2 Hz); 2.23 (dd, 1 H, CH$_a\underline{H}_b$CH=, J = 3.8 Hz, J = 18.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6), δ*: 134.27; 131.74; (130.45, 129.65, 129.49, 128.64); (128.92, 128.14, 127.99, 127.16); 126.97; (127.39, 126.59, 126.48, 126.39, 125.56) 2C; 124.26; (49.09, 48.66, 48.50, 48.08); (44.07, 43.76, 43.50, 43.20); (32.65, 32.58, 32.49); 30.81.

X-ray diffraction analysis of compound **2a** ($C_{15}H_{17}BrN$) was carried out at 100 K on a Smart APEX2 CCD automatic three-circle diffractometer (Mo-Kα radiation, graphite monochromator, ω scan mode, $2\theta_{max} \le 58°$). At 100 K, crystals are monoclinic: a = 11.175(2) Å, b = 13.603(4) Å, c = 9.601(3) Å, β = 112.666(7)°, V = 1346.8(7) Å^3, d_{calc} = 1.436 g cm^{-3}, M = 291.21, $F(000)$ = 596, μ = 30.30 cm^{-1}, Z = 4 (Z' = 1), space group $P2_1/c$. The total number of measured reflections was 10 020 (R_{int} = 0.0349). In further calculations and refinement, 3565 independent reflections were used. The structure was solved by the direct method and refined by the least-squares method in the anisotropic full-matrix approximation on F^2_{hkl}. The hydrogen atoms were located from electron-density difference maps and refined isotropically. Final residuals are R = 0.0299 for 2694 reflections with $I > 2\sigma(I)$, wR_2 = 0.0772, and GOOF = 0.940 for all reflections. All calculations were performed with the SHELXTL PLUS program package.[11]

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* Most signals in the ^{13}C NMR spectrum are split. This splitting (given in parentheses[4]) is probably due to the dynamic behavior of the bicyclic molecule.

References

1. (a) G. A. Cordell, *Introduction to Alkaloids, A Biogenetic Approach*; Wiley-Interscience, New York, 1981; (b) M. Lounasmaa and T. Tamminen, in *The Alkaloids, the Tropane Alkaloids*, Academic Press, New York, 1993, Vol. **44**, 1; (c) S. Singh, *Chem. Rev.*, 2000, **100**, 925; (d) K. L. Swanson and E. X. Albuquerque, *Handbook Expt. Pharmacology*, Vol. **102**, *Selective Neurotoxicity*, Eds H. Herken and F. Hucho, Springer Verlag, Berlin—Heidelberg, 1992, 620.
2. (a) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413; (b) A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3012; (c) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127; (d) A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199.
3. (a) C. E. Neipp and S. F. Martin, *Tetrahedron Lett.*, 2002, **43**, 1779; (b) T. Itoh, N. Yamazaki, and C. Kibayashi, *Org. Lett.*, 2002, **4**, 2469; (s) C. E. Neipp and S. F. Martin, *J. Org. Chem.*, 2003, **68**, 8867; (d) J. B. Brenneman and S. F. Martin, *Org. Lett.*, 2004, **6**, 1329; (e) V. K. Aggarwal, C. J. Astle, and M. Rogers-Evans, *Org. Lett.*, 2004, **6**, 1469.
4. N. Yu. Kuznetsov, V. N. Khrustalev, I. A. Godovikov, and Yu. N. Bubnov, *Eur. J. Org. Chem.*, 2006, 113.
5. P. Nieczypor, J. C. Mol, N. B. Bespalova, and Yu. N. Bubnov, *Eur. J. Org. Chem.*, 2004, **7**, 812.
6. (a) J. Quick, C. Mondello, M. Humora, and T. Brennan, *J. Org. Chem.*, 1978, **43**, 2705; (b) Y. Mikata, *Acta Crystallogr., Sect. C, Cryst. Struct. Commun.*, 1997, **53**, 1486.
7. (a) F. V. Pastukhov, I. V. Yampolsky, and Yu. N. Bubnov, *J. Organomet. Chem.*, 2002, **657**, 123; (b) W. Baik, W. Luan, H. J. Lee, C. H. Yoon, S. Koo, and B. H. Kim, *Can. J. Chem.*, 2005, **83**, 213.
8. (a) Yu. N. Bubnov, *Adv. Boron Chemistry*, Ed. W. Siebert, 1997, 123; (b) Yu. N. Bubnov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1203 [*Russ. Chem. Bull.*, 1995, **46**, 1156 (Engl. Transl.)]; (c) Yu. N. Bubnov, E. E. Demina, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1361 [*Russ. Chem. Bull.*, 1997, **46**, 1306 (Engl. Transl.)].
9. (a) Yu. N. Bubnov, E. V. Klimkina, and A. V. Ignatenko, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 1206 [*Russ. Chem. Bull.*, 1998, **47**, 1175 (Engl. Transl.)]; (b) Yu. N. Bubnov and E. V. Klimkina, *Chem. Heterocycl. Compd.*, 1999, **35**, 888.
10. G. Majetich, S. Liu, J. Fang, D. Siesel, and Y. Zhang, *J. Org. Chem.*, 1997, **62**, 6928.
11. G. M. Sheldrick, *SHELXTL-97, Ver. 5.10*, Bruker AXS Inc., Madison (WI-53719, USA), 1997.

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