Functionalization of *N-tert*-butoxycarbonyl-7- and *N-tert*-butoxycarbonyl-8-bromo-10-azabicyclo[4.3.1]deca-3,7-dienes. A route to a ferruginine homolog*

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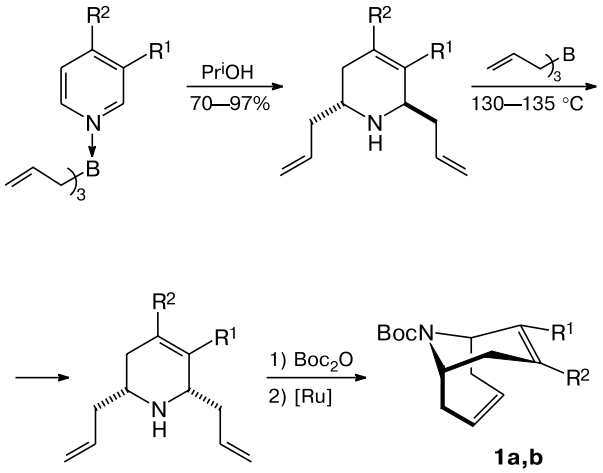
N-tert-Butoxycarbonyl-7- and *N-tert*-butoxycarbonyl-8-bromo-10-azabicyclo[4.3.1]deca-3,7-dienes are convenient substrates for further modification using replacement of the Br atom by a cyano group or a Li atom. Treatment of lithium derivatives with dimethylformamide and *N*-methoxy-*N*-methylacetamide gave the corresponding α,β-unsaturated aldehydes (67—84%) and ketones (~70%). Ketone **4b** is a direct precursor of a homolog of the alkaloid ferruginine.

Key words: nitrogen heterocycles, bromopyridines, *cis*- and *trans*-2,6-diallyl-3-piperideines, *trans/cis* isomerization, metathesis, vinyl bromides, acylation, ferruginine.

Bridged azabicyclic compounds exhibit a broad spectrum of biological activity.[1] Recently, we have developed an efficient method of designing various bridged azabicycles, including 7- and 8-bromo-10-azabicyclo[4.3.1]-deca-3,7-dienes (**1a,b**), starting from substituted pyridines, isoquinolines, and pyrrole. This method involves a combination of diallylboration and intramolecular metathesis.[2] The conditions of the synthesis allows such an important functional group as vinylic bromide to be retained in heterocycles (Scheme 1).

Scheme 1



R^1 = H, R^2 = Br (**1a**), R^1 = Br, R^2 = H (**1b**)

* Dedicated to Academician G. A. Abakumov on the occasion of his 70th birthday.

In the present work, we described the synthesis of formyl-, acetyl-, and cyano-10-azabicyclo[4.3.1]deca-3,7-dienes from earlier prepared bromides **1a,b**. We demonstrated the possibility of constructing the framework of a homolog of the alkaloid ferruginine. Ferruginine itself is highly neuroactive and is being investigated for treatment of Alzheimer´s disease.[1c]

Results and Discussion

The presence of the vinylic Br atom in compounds **1a,b** allows their modification. One way involves replacement of the Br atom by a cyano group. A reaction of compound **1a** with CuCN (3 equiv.)[3] in *N*-methylpyrrolidone (NMP) gave nitrile **2a** in 42% yield (Scheme 2).

Alternatively, the Br atom can be replaced by lithium. The action of Bu^tLi in Et_2O—THF on compounds **1a,b** at −78 °C followed by treatment of the resulting lithium derivatives with dimethylformamide and hydrolysis gave the corresponding aldehydes **3a** and **3b** in 67 and 84% yields, respectively (Schemes 2, 3). The high yield of compound **3b** can be associated with more efficient lithiation, probably because of the directing effect of the Boc-protecting group. Such an effect is highly probable since coordination of the Boc group with the Li atom can produce a six-membered ring, while in the case of compound **1a**, this coordination is impossible.

Treatment of lithium derivative (**1b**-Li) with *N*-methoxy-*N*-methylacetamide (Weinreb´s amide)[4] afforded dienone **4b** (70%). The use of other reagents (dimethylacetamide, ethyl acetate, Ac_2O, or acetonitrile) led only to trace amounts of ketone **4b**. In the series of the

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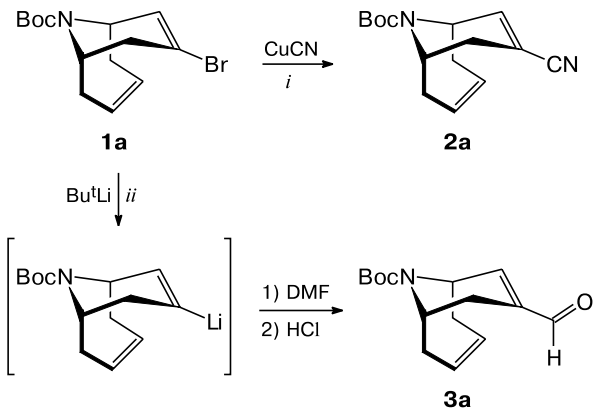
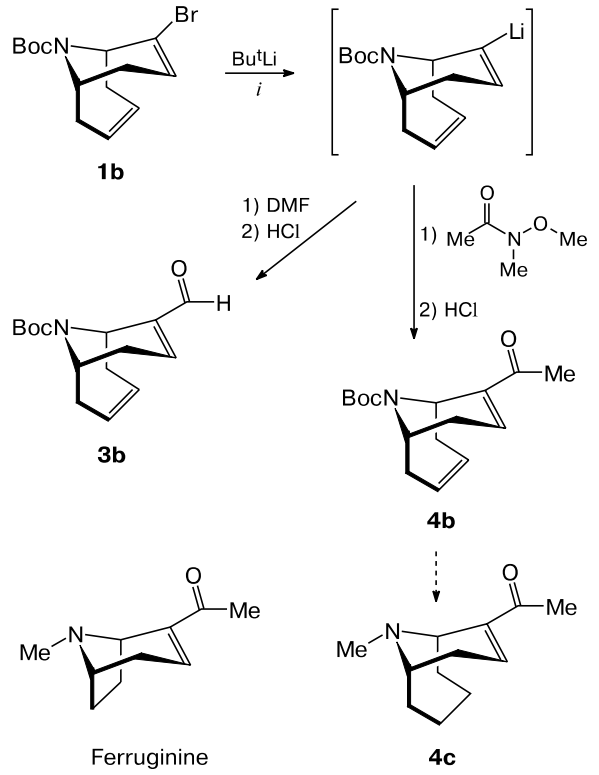
Scheme 2



Reagents and conditions: *i*. NMP, 150 °C, 4 h. *ii*. Bu^{t}Li (2 equiv.), Et_2O/THF, −78 °C.

Scheme 3



Reagents and conditions: *i*. Bu^{t}Li (2 equiv.), Et_2O/THF, −78 °C.

tropane bicycles, a transformation of compounds of the type **4b** into ferruginine homologs (**4c**) is a well-developed process[5] involving selective reduction of the inactivated C=C bond in the presence of $RhCl(Ph_3P)_3$, removal of the protecting group, and reductive N-methylation.

In conclusion, we discovered convenient ways of modifying bridged bromoazabicycles and proposed a strategy of the synthesis of a homolog of the alkaloid ferruginine.

Experimental

Reactions were carried out under purified argon. All solvents were purified and dried according to standard procedures. NMR spectra were recorded on Bruker Avance-300, Bruker Avance-400, and Bruker Avance-600 spectrometers. Mass spectra were recorded on a Finnigan Polaris Q Ion Trap instrument. Column chromatography was carried out on silica gel (60—230 mesh, Merck). Compounds **1a,b** were prepared as described earlier.[2a]

***N-tert*-Butoxycarbonyl-8-cyano-10-azabicyclo[4.3.1]deca-3,7-diene (2a).** Cuprous cyanide (0.27 g, 3.0 mmol) was added to a solution of bromide **1a** (0.31 g, 1.0 mmol) in *N*-methylpyrrolidone (5 mL). The reaction mixture was heated at 150 °C for 4 h, cooled to 20 °C, and diluted with water (25 mL) and brine (10 mL). The product was extracted with *n*-hexane—Et_2O (2 : 1) (3×10 mL). The combined extracts were dried with K_2CO_3, the solvent was removed under reduced pressure, and the residue was chromatographed in *n*-hexane—EtOAc (10 : 1). The yield of compound **2a** was 0.11 g (42%), oil. Found (%): C, 69.30; H, 7.79; N, 10.67. $C_{15}H_{20}N_2O_2$. Calculated (%): C, 69.20; H, 7.74; N, 10.76. The signals in the NMR spectra are broadened and doubled because of hindered rotation of the amide group. ^{1}H NMR (400 MHz, C_6D_6), δ: 5.34 (br.s, 1 H); 5.15 (br.m, 1 H); 4.91 (br.m, 1 H); 4.95, 4.14 (both br.s, 1 H total); 4.23, 3.88 (both m, 1 H total); 2.26 (br.d, 0.53 H, J = 16.9 Hz); 2.08—1.98 (two overlapping br.d, 1 H total); 1.87 (br.d, 0.5 H, J = 15.5 Hz); 1.76, 1.73 (both dt, 1 H total, J = 2.6 Hz, J = 8.0 Hz); 1.48—1.42 (m, 0.82 H); 1.38—1.32 (m, 0.84 H); 1.26—1.07 (m, 1.4 H); 1.13 (br.s, 9 H). ^{13}C NMR (100 MHz, C_6D_6), δ: 153.85; 142.94, 141.81; 128.76, 128.31; 127.68, 127.13; 118.16; 110.91, 110.23; 79.56; 48.93, 47.87; 44.71, 43.16; 35.30, 34.76; 33.14, 32.59; 30.10 (2 C); 28.13 (3 CH_3). MS (EI, 70 eV), m/z: 261 $[MH]^+$ (7); 205 (20); 204 (35); 187 (37); 159 (45); 149 (30); 119 (20); 105 (100); 80 (65); 57 (23).

***N-tert*-Butoxycarbonyl-8-formyl-10-azabicyclo[4.3.1]deca-3,7-diene (3a).** A 1.7 *M* solution of Bu^{t}Li in *n*-pentane (2.5 mL, 4.2 mmol) was added dropwise at −78 °C to a solution of bromide **1a** (0.62 g, 2.0 mmol) in Et_2O—THF (1 : 1, 12 mL). The mixture was stirred for 2.5 h. Then a solution of dimethylformamide (0.44 mL, 6.0 mmol) in Et_2O (1 mL) was added dropwise. The mixture was stirred at the same temperature for 10 min and treated with 3 *M* HCl (2 mL, 6.0 mmol) at 20 °C. The organic layer was washed with brine, dried with K_2CO_3, and concentrated under reduced pressure. The residue was chromatographed in *n*-hexane—EtOAc (8 : 1). The yield of compound **3a** was 0.35 g (67%), m.p. 41—42 °C. Found (%): C, 68.47; H, 8.09; N, 5.16. $C_{15}H_{21}NO_3$. Calculated (%): C, 68.42; H, 8.04; N, 5.32. The signals in the NMR spectrum are doubled because of hindered rotation of the amide group. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.52, 9.50 (both s, 1 H total); 6.60, 6.54 (both d, 1 H total, J = 3.2 Hz); 5.76—5.72, 5.51—5.48 (both m, 2 H total); 5.16, 5.00 (both br.s, 1 H total); 4.79—4.73, 4.64—4.59 (both m, 1 H total); 2.87—2.73 (m, 1 H); 2.61—2.15 (m, 5 H); 1.54, 1.53 (both s, 9 H total).

***N-tert*-Butoxycarbonyl-7-formyl-10-azabicyclo[4.3.1]deca-3,7-diene (3b)** was obtained analogously from bromide **1b**. The yield was 0.39 g (84%), oil. Found (%): C, 68.40; H, 8.07; N, 5.26. $C_{15}H_{21}NO_3$. Calculated (%): C, 68.42; H, 8.04; N, 5.32. The signals in the NMR spectra are broadened and doubled because of hindered rotation of the amide group. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.34 (s, 1 H); 6.95, 6.90 (both s, 1 H total); 5.74 (br.m, 1 H); 5.52 (br.m, 1 H); 5.24, 5.07 (both s, 1 H total); 4.71, 4.59 (both m, 1 H total); 2.81, 2.75 (both d, 1 H total, J = 8.2 Hz); 2.56—2.49 (m, 3 H); 2.32—2.23 (m, 2 H); 1.52 (br.s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 191.37, 191.00; 154.47, 154.23; 150.10, 148.92; 140.56, 140.19; 130.30, 129.48; 128.48, 127.73; 80.23, 79.99; (46.66, 45.59, 44.19) (2 C); 36.19, 35.73; 33.16, 32.78; 30.78 (2 C); 28.50 (3 CH_3).

***N-tert*-Butoxycarbonyl-7-acetyl-10-azabicyclo[4.3.1]deca-3,7-diene (4b).** A 1.7 *M* solution of Bu^tLi in *n*-pentane (2.5 mL, 4.2 mmol) was added dropwise at −78 °C to a solution of bromide **1b** (0.62 g, 2.0 mmol) in Et_2O—THF (1 : 1, 12 mL). The mixture was stirred for 2.5 h. Then a solution of *N*-methoxy-*N*-methylacetamide (0.41 g, 4.0 mmol) in Et_2O (1 mL) was added dropwise. The mixture was successively stirred at −70 (1 h), −50 (1 h), and 20 °C (10 h) and treated with 3 *M* HCl (2 mL, 6.0 mmol). The organic layer was washed with brine, dried with K_2CO_3, and concentrated under reduced pressure. The residue was chromatographed in *n*-hexane—EtOAc (5 : 1), R_f = 0.2. The yield of compound **4b** was 0.39 g (70%), an oil. Found (%): C, 69.31; H, 8.40; N, 4.97. $C_{16}H_{23}NO_3$. Calculated (%): C, 69.29; H, 8.36; N, 5.05. The signals in the NMR spectra are broadened and doubled because of hindered rotation of the amide group. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.95, 6.90 (both s, 1 H total); 5.66 (br.m, 1 H); 5.41 (br.m, 1 H); 5.18, 5.03 (both s, 1 H total); 4.55, 4.41 (both m, 1 H total); 2.64, 2.58 (both dd, 1 H total, J = 2.1 Hz, J = 8.1 Hz); 2.55—2.36 (m, 3 H); 2.20, 2.18 (both s, 3 H total); 2.14—2.06 (m, 2 H); 1.41—1.40 (both s, 9 H total). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 196.37, 195.97; 154.55, 154.25; 140.49, 139.53; 138.76, 138.40; 130.64, 129.88; 128.39, 127.70; 79.86, 79.63; 46.92, 45.89; 44.91, 43.74; 35.98, 35.52; 33.56, 33.18; 30.30 (2 C); 28.46 (3 CH_3); 25.19, 25.10. MS (EI, 70 eV), m/z: 277 $[M]^+$ (1.0); 221 (7); 204 (12); 177 (23); 162 (15); 134 (10); 122 (82); 80 (100); 57 (5); 41 (15).

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