Construction of mononitrogen heterocycles with a combined system of 1-azaspiro[4.n]alkene and 3-benzazocine fragments through the intramolecular eight-membered Heck cyclization

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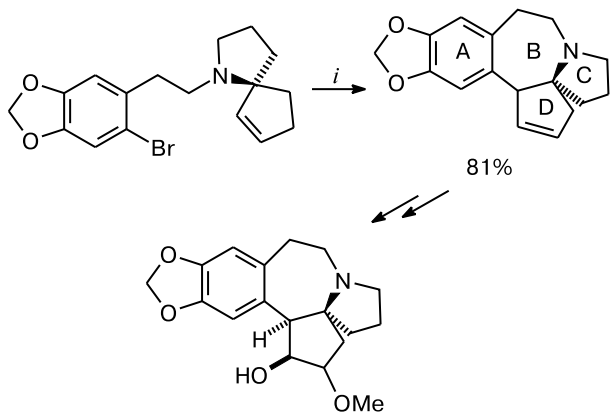
Amides, obtained from 1-azaspiro[4.n]alkenes (n = 3, 4, 5) and 2-(6-bromo-1,3-benzodioxol-5-yl)acetyl chloride, upon heating with a Herrmann—Beller palladium catalyst undergo intramolecular cyclization by the Heck reaction to form pentacyclic compounds (up to 94% yield) including an 1-azaspiro[4.n]alkene (n = 4, 5) fragment and a new eight-membered 3-benzazocine ring. The structure of the thus obtained pentacycles with the 1-azaspiro[4.4]non-7-ene fragment is isomeric to the structure of the main core of alkaloid cephalotaxine. In the case of 1-azaspiro[4.5]dec-2-ene derivative, the reaction is accompanied by the reduction of bromo amide, with the yield of the cyclization product being 34%. The starting 1-azaspiro-[4.n]alkenes (n = 3, 4, 5) were synthesized by the reductive diallylboration of 3-chloropropionitrile or the corresponding lactams (piperidin-2-one, (*2S*)-2-hydroxymethyl- and 5,5-dimethylpyrrolidin-2-one) with subsequent intramolecular metathesis upon the action of Grubbs catalyst.

Key words: 3-benzazocine, allylboration, metathesis, the Heck reaction, palladacycle, Cephalotaxine, spiro compounds, medium-sized rings.

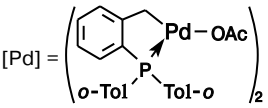
Seven- and eight-membered azaheterocycles are the structural fragments of many alkaloids and biologically active compounds possessing pharmacologically useful properties.[1—3] At the same time, it is known for a long time that the use of cyclization reactions and other traditional methods of organic chemistry for the construction of medium-sized (seven- and eight-membered) rings is inefficient due to the unfavorable enthalpy and entropy factors.[4] At the same time, metal complex catalysis[5] and especially metathesis reactions of dienes with terminal multiple bonds and the Heck cyclization reaction[6] allows one to obtain a wide variety of compounds of this type.

Alkaloid cephalotaxine (CPT) is one of the natural compounds containing 3-benzazepine (seven-membered) ring, it is produced by yew-trees growing in China and Japan (*Cephalotaxus harrigtonia* and *fortunei* var. *Drupacea*). Esters of CPT (*harringtonines*) possess high antileucemia (myeloid leukemia, clinical trials)[7a,b] and antimalaria activity.[7c] Therefore, preparation of both CPT and its structural analogs is an actual problem. The presence of a spiro-joint system bound to the benzazepine ring is another characteristic feature of a CPT molecule. To form the B, C, and D system of rings of a CPT molecule, two palladium catalyzed cyclizations (allylic amination and the Heck reaction) were successfully used[7d] (Scheme 1). The same methodology were applied[7e,f] for obtaining a number of close structural analogs of CPT with B, C, and D rings of various sizes. Attempts to use this approach for the synthesis of the eight-membered ring B were unsuccessful.

Scheme 1



i. 4 mol.% [Pd], Bu_4NOAc, MeCN/DMF/H_2O, 110—120 °C, 10 h;



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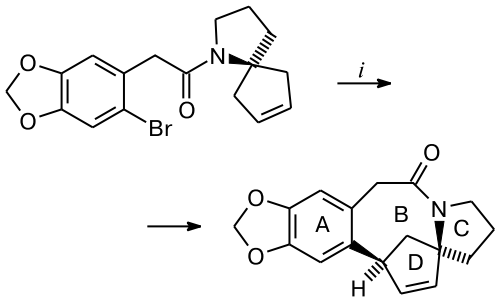
During accomplishing our program on the use of allylic boranes in the synthesis of heterocyclic compounds,[8] we have developed an efficient method for obtaining 1-azaspiro[4.n]alkenes based on the diallylboration of lactams with subsequent intramolecular metathesis (RCM) of diallylated products.[8c] This method was used for the synthesis of spiranes with five-, six-, seven-, and 13-membered azacycles, that henceforth allowed us to develop a formal total synthesis of (±)-cephalotaxine.[9] Our first attempt to use the Heck reaction for the construction of the azepine ring B of the cephalotaxine core led to a discovery of a new cyclization, whose product was a structural isomer of the CPT core with the 3-benzazocine eight-membered ring B (Scheme 2).[10]

Scheme 2



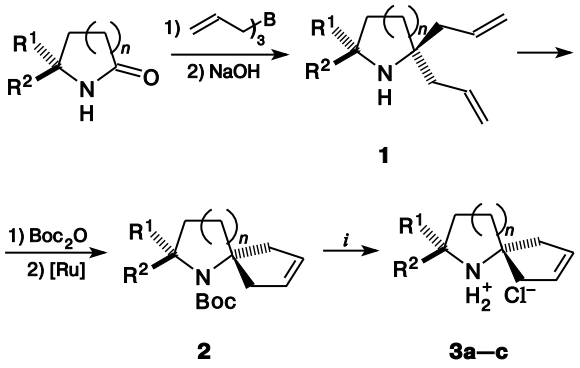
Reagents and conditions: 5 mol.% [Pd], MeCN—DMF—H_2O, NaOAc, 140 °C, 13 h.

Developing this area, we have synthesized a series of 1-azaspiro[4.n]alkenes and accomplished their cyclization upon the action of a palladium catalyst (by the Heck reaction). This resulted in obtaining new 3-benzazocine derivatives with five- and six-membered azacycle C and different substituents in the spiro fragment, that indicates a general character of the cyclization.

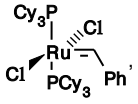
Starting from (*2S*)-2-hydroxymethylpyrrolidin-, 5,5-dimethylpyrrolidin-, piperidin-2-one and 3-chloropropionitrile, derivatives of 1-azaspiro[4.n]alkenes with four-, five-, and six-membered azacycle (**3a—c**)[9] were obtained (Schemes 3 and 4).

The reaction of lactams containing an N—H bond with triallylborane leads to diallylated heterocycles **1**. The latter were further transformed to *N*-Boc-derivatives **2** with subsequent intramolecular cyclization (RCM) in the presence of a Grubbs catalyst [Ru]. Removal of the protecting group in **2** was carried out upon the action of HCl in dioxane, that gave the corresponding hydrochlorides **3** in 83—99% yield. Azetidine derivative **2** ($R^1 = R^2 = H$, $n = 0$) was an exception, which decomposed upon the action of strong acids. Hydrochlorides **3a—c** were acylated with 2-(6-bromo-1,3-benzodioxol-5-yl)acetyl chloride **4** by the

Scheme 3



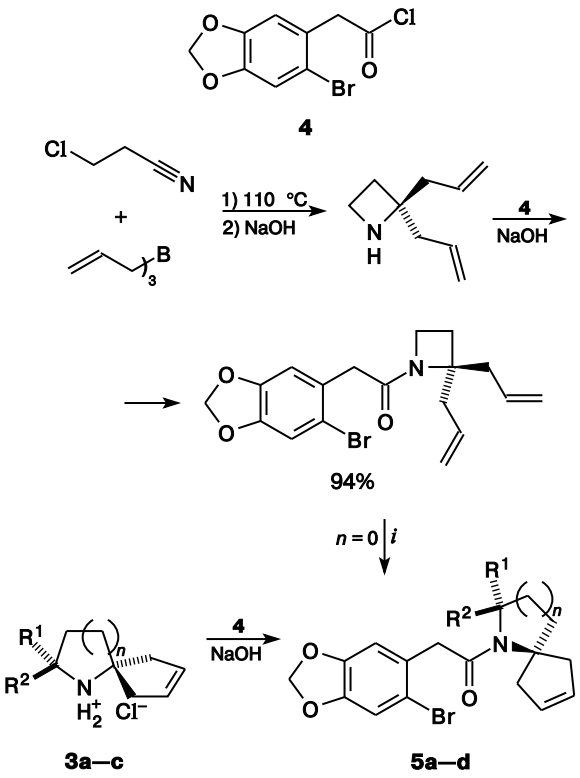
i. HCl, dioxane.

[Ru] = 

Compound	R^1	R^2	n	Yield (%)
3a	CH_2OH	H	1	99
3b	Me	Me	1	83
3c	H	H	2	97

Cy is cyclohexyl

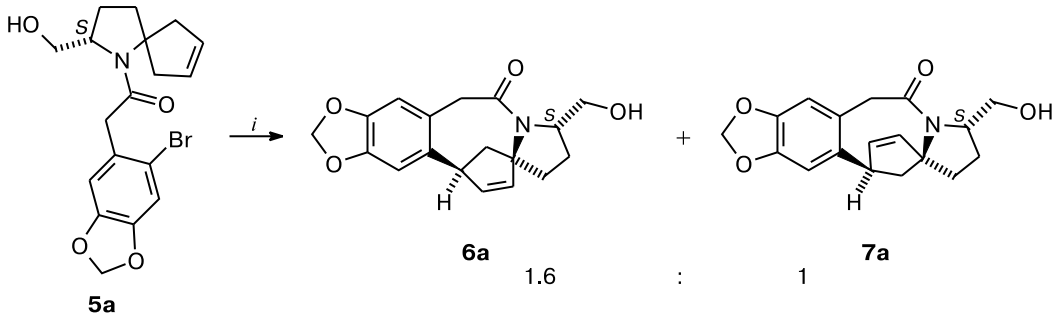
Scheme 4



i. 1 mol.% [Ru], CH_2Cl_2.

Compound	R^1	R^2	n	Yield (%)
5a	CH_2OH	H	1	96
5b	Me	Me	1	83
5c	H	H	2	94
5d	H	H	0	91

Scheme 5



i. 5 mol.% [Pd], DMF/MeCN/H_2O, 125 °C, 5 h. 82% total yield.

Schotten—Baumann reaction (20% aq. NaOH, CH_2Cl_2) (Scheme 4), and the amides **5a**—**c** formed were isolated in 83—96% yield by crystallization or chromatography. Amide **5d** was synthesized by acylation of 2,2-diallylazetidine and subsequent metathesis reaction (see Scheme 4).

The amides **5a**—**d** obtained underwent cyclization by the Heck reaction[10] in the presence of the Hermann—Beller palladacycle [Pd] in catalytic amount (its structure is given in Scheme 1). Cyclization of chiral amide **5a** with 2-hydroxymethyl substituent leads to diastereomeric alcohols **6a** and **7a** (Scheme 5) in the ratio 1.6 : 1 (according to the ^{1}H NMR spectra of the reaction mixture), that indicates an insignificant effect of the substituent on the diastereoselectivity of the process. The cyclization of **5a** reaches completion within 5 h at 125 °C, whereas the cyclization of unsubstituted amide (see Scheme 2) requires more drastic conditions (140 °C, 13 h).[10] This effect can be explained by the formation of hydrogen bonds between the oxygen atom of the carboxamide group and the hydroxy group, that leads to some stabilization of such conformation of molecule **5a**, which is favorable for the cyclization.

The structure of the major isomer of **6a** was established by X-ray diffraction (Fig. 1). The eight-membered ring in compound **6a** has the chair conformation with the planar central fragment C(1)—C(20)/C(11)—C(12). This compound has three asymmetric centers at the C(1), C(14), and C(17) atoms with known (*S*)-configuration at the C(14) atom, and it crystallizes in the $P2_12_12_1$ chiral space group. Thus, the asymmetric centers have the (1*R*,14*S*,17*S*) absolute configuration. In crystal, the molecules are bound through the intermolecular hydrogen bonds O—H...O (O(1)—H(10)...O(12) ($x + 1/2, -y + 3/2, -z + 1$), O...O 2.820(1), H...O 2.05 Å, O—H...O 158°). The bond distances and angles in the molecule have standard values.

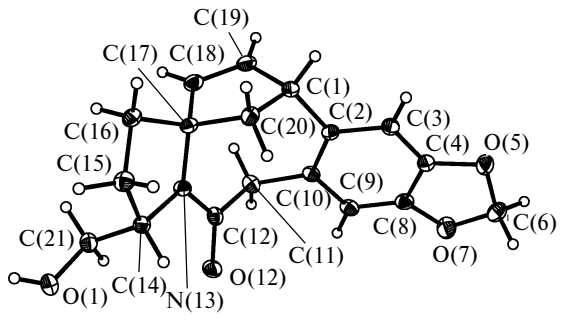
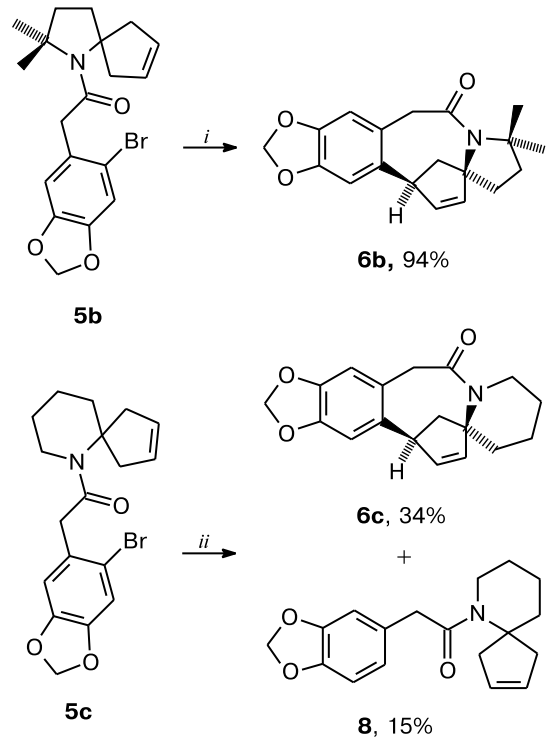


Fig. 1. Molecular structure of **6a** is represented by ellipsoids of thermal vibrations with 50% probability.

2,2-Dimethyl-substituted amide **5b** also readily gives cyclization product **6b** (Scheme 6), which after chromato-

Scheme 6



Reagents and conditions: 5 mol.% [Pd], DMF—MeCN—H_2O, 125 °C; 10 h (*i*); 16 h (*ii*).

graphic purification was isolated in crystalline form in 94% yield.

Unsubstituted amide **5c** with the six-membered (piperidine) ring in the spiro fragment undergoes the cyclization much less efficiently: together with pentacyclic product **6c** (34%), a reduced amide **8** was obtained in 15% yield (see Scheme 6). Our attempts to carry out the cyclization of amide **5d** containing a four-membered ring (azetidine derivative) were unsuccessful: in all the cases, an unseparable mixture of compounds, apparently, decomposition products, was obtained.

In conclusion, we discovered a new type of cyclization by the Heck reaction. Amides **5a—c** upon heating (125 °C) in the presence of the Hermann—Beller[7g] palladacycle [Pd] (see Scheme 1) undergo the eight-membered cyclization to form pentacyclic compounds **6a—c** and **7a** containing a 3-benzazocine fragment. The cyclization is the most efficient (80—94%) for amides **5a**,**b** including a 1-azaspiro[4.4]non-7-ene system; the structure of the pentacycles obtained is isomeric to the structure of the main core of alkaloid cephalotaxine. Note that chiral amide **5a** containing a hydroxymethyl group is a prospective model substrate for the study of activity of chiral catalysts of the Heck reaction.

Experimental

2,2-Diallylazetidine and the corresponding *N*-Boc-protected spiranes **2** were obtained according to the procedures described earlier.[8,9] NMR spectra were recorded on a Bruker AMX-400 and Bruker Avance-300 spectrometers. Mass spectra were recorded on a Finnigan Polaris Q Ion Trap instrument. Column chromatography was performed using 60—230 mesh silica gel (Merck). Elemental analysis was performed on a Carlo-Erba 1106 automatic analyser. Grubbs catalyst [Ru] was purchased from Aldrich. Hermann—Beller palladacycle [Pd] was prepared from palladium acetate and tri-*o*-tolylphosphine according to the known procedure.[7g]

(2*S*)-1-Azaspiro[4.4]non-7-en-2-ylmethanol hydrochloride (3a). A solution of HCl in dioxane (5.06 *M*, 1.26 mL, 6.4 mmol) was added to a solution of *N*-Boc-protected (2*S*)-1-azaspiro-[4.4]non-7-en-2-ylmethanol[9] (0.65 g, 2.56 mmol) in dioxane (2 mL), the mixture obtained was heated at 70 °C for 40 min (TLC monitoring, *n*-hexane : EtOAc = 1 : 1). After the reaction reached completion, the mixture was diluted with Et_2O (5 mL) and left to crystallize, a precipitate formed was filtered off and dried *in vacuo* to obtain **3a** (0.48 g, 99%) as white crystals, m.p. 112.5—113.5 °C, $[\alpha]_D^{25}$ +12.8 (*c* = 1; MeOH). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 9.80 (br.s, 1 H, NH_2^+); 9.06 (br.s, 1 H, NH_2^+); 5.74—5.70 (m, 2 H, CH=); 5.43 (br.s, 1 H, OH); 3.76—3.60 (m, 3 H, C<u>H</u>$_2$OH and C<u>H</u>NH_2^+); 2.99 (d, 1 H, C<u>H</u>$_2$CH=, *J* = 17.4 Hz); 2.84 (d, 1 H, C<u>H</u>$_2$CH=, *J* = 17.2 Hz); 2.48 (dm, 2 H, C<u>H</u>$_2$CH=, *J* = 16.1 Hz); 2.07 (dddd, 1 H, C<u>H</u>$_a$H$_b$CHN, *J* = 5.7 Hz, *J* = 7.1 Hz, *J* = 8.3 Hz, *J* = 16.3 Hz); 1.96 (m, 2 H, CH_2C); 1.86—1.77 (m, 1 H CH$_a$<u>H</u>$_b$CHN). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 133.65; 133.36; 77.09; 65.21; 65.31; 47.26; 47.07; 41.65; 29.88. MS (70 eV, EI): *m*/*z* 154 [M^+ – Cl] (2); 153 [M^+ – HCl] (8); 122 (30); 108 (21); 105 (20); 94 (40); 93 (23); 92 (100); 91 (96); 80 (50); 79 (46); 77 (59); 51 (16); 41 (33); 39 (36). Found (%): C, 56.98; H, 8.61; N, 7.41. $C_9H_{16}NOCl$ (189.7). Calculated (%): C, 56.99; H, 8.50; N, 7.38.

2,2-Dimethyl-1-azaspiro[4.4]non-7-ene hydrochloride (3b). *N*-Boc-Protected 2,2-dimethyl-1-azaspiro[4.4]non-7-ene[9] (1.03 g, 4.1 mmol) was treated with a solution of HCl in dioxane (5.06 *M*, 2 mL, 10.2 mmol) at 70 °C for 30 min as in the case of **3a** to obtain **3b** (0.64 g, 83%) as brown crystals, m.p. >260 °C (with decomp.). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.53 (br.s, 2 H, NH_2^+); 5.61 (s, 2 H, CH=); 3.35 (d, 2 H, C<u>H</u>$_2$CH=, *J* = 15.5 Hz); 2.47 (d, 2 H, C<u>H</u>$_2$CH=, *J* = 15.5 Hz); 2.07 (t, 2 H, CH_2, *J* = 7.3 Hz); 1.87 (t, 2 H, CH_2C, *J* = 7.3 Hz); 1.56 (s, 6 H, 2Me). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 128.39; 72.83; 65.07; 44.60; 38.23; 37.97; 27.26. MS (70 eV, EI): *m*/*z* 151 [M^+ – HCl] (32); 137 (10); 136 [M^+ – HCl – CH_3] (100); 119 (20); 108 (12); 95 (23); 94 (89); 91 (26); 82 (40); 80 (22); 79 (21); 77 (24); 67 (16); 51 (10); 49 (30). Found (%): C, 63.94; H, 9.72; N, 7.69. $C_{10}H_{18}NCl$ (187.7). Calculated (%): C, 63.99; H, 9.67; N, 7.46.

6-Azaspiro[4.5]dec-2-ene hydrochloride (3c). *N*-Boc-Protected 6-azaspiro[4.5]dec-2-ene[8] (1.07 g, 4.5 mmol) was treated with a solution of HCl in dioxane (5.37 *M*, 1.87 mL, 10.0 mmol) at 70 °C for 30 min as in the case of **3a** to obtain **3c** (0.72 g, 97%) as beige crystals, m.p. 185—186 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.55 (br.s, 2 H, NH_2^+); 5.61 (s, 2 H, CH=); 3.06 (br.s, 2 H, CH_2N); 2.85 (d, 2 H, C<u>H</u>$_2$CH=, *J* = 15.9 Hz); 2.47 (d, 2 H, C<u>H</u>$_2$CH=, *J* = 15.8 Hz); 1.83 (br.s, 4 H, 2CH_2); 1.62—1.61 (m, 2 H, CH_2C). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 127.72; 64.16; 42.54; 41.79; 33.83; 21.63; 19.51. MS (70 eV, EI): *m*/*z* 137 [M^+ – HCl] (45); 136 (72); 134 (12); 123 (12); 122 (96); 110 (17); 109 (19); 108 (59); 96 (20); 95 (54); 94 (100); 93 (30); 91 (33); 82 (27); 80 (72); 79 (23); 77 (30); 67 (21); 54 (17); 39 (12). Found (%): C, 62.21; H, 9.32; N, 7.99. $C_9H_{16}NCl$ (173.7). Calculated (%): C, 62.24; H, 9.29; N, 8.06.

{(2*S*)-1-[(6-Bromo-1,3-benzodioxol-5-yl)acetyl]-1-azaspiro-[4.4]non-7-en-2-yl}methanol (5a). Acyl chloride **4** (0.34 g, 1.23 mmol) was added to a solution of **3a** (0.22 g, 1.16 mmol) in CH_2Cl_2 (5 mL) at 0 °C, followed by immediate addition of 20% aqueous NaOH (1.0 mL, 6.2 mmol) with vigorous stirring. The reaction progress was monitored by TLC (*n*-hexane : EtOAc = = 1 : 2, R_f (**5a**) = 0.4). Powdered K_2CO_3 (3 g) was added to the reaction mixture, a suspension obtained was filtered, washed with CH_2Cl_2. The filtrate was concentrated at reduced pressure, a residual oil was subjected to chromatography in the *n*-hexane : EtOAc = 1 : 2 system to obtain **5a** (0.44 g, 96%) as an oil, $[\alpha]_D^{25}$ –6.0 (*c* = 1; $CHCl_3$). *Due to the hindered rotation in the amide group, doubling, overlap, and broadening of some signals are observed in the NMR spectra.* ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.96 and 6.94 (both s, total 1 H, $(HC=)_{arom}$); 6.75 and 6.71 (both s, total 1 H, $(HC=)_{arom}$); 5.92 and 5.90 (both s, total 2 H, OCH_2O); 5.72 and 5.61—5.55 (s and m, total 2 H, CH=); 4.45—4.41 (m, 0.73 H); 4.07—4.04 (m, 0.69 H); 3.80 and 3.75 (both s, total 0.68 H); 3.71—3.62 (m, 1.29 H); 3.60 and 3.56 (both s, total 0.75 H); 3.55—3.54 (m, 0.59 H); 3.48—3.39 (m, 0.71 H); 3.35 (d, 0.66 H, *J* = 16.2 Hz); 3.15—2.84 (m, 2 H); 2.64—2.51 (m, 0.76 H); 2.10—1.89 (m, 5 H); 1.72—1.67 (m, 0.4 H). ^{13}C NMR (100 MHz, C_6D_6), δ: 172.52; 168.78; 147.36; 147.31; 147.28; 129.26; 129.18; 128.87; 128.77; 128.39; 128.23; 115.19; 115.07; 112.64; 112.47; 111.34; 110.87; 101.78; 101.68; 70.61; 68.91; 67.14; 63.58; 63.24; 60.88; 48.67; 47.63; 44.78; 44.37; 44.11; 42.50; 41.03; 40.99; 25.71; 25.61. MS (70 eV, EI): *m*/*z* 395/393 [M^+] (9); 327 (37); 314 (94); 271 (50); 269/267 (15);

254 (64); 247 (46); 215 (56); 213 (36); 210 (41); 204 (32); 189 (43); 169 (25); 166 (22); 149 (69); 141/139 (10); 136/134 (12); 133 (26); 123 (25); 122 (100); 121 (20); 119 (36); 105 (51); 99 (20); 97 (31); 95 (35); 93 (32); 91 (42); 85 (49); 81/79 (43); 71 (50); 67 (43); 57 (75); 55 (36). Found (%): C, 56.14; H, 7.09; N, 4.00; Br, 23.28. $C_{18}H_{20}NO_4Br$ (394.3). Calculated (%): C, 54.84; H, 5.11; N, 3.55; Br, 20.27.

1-[(6-Bromo-1,3-benzodioxol-5-yl)acetyl]-2,2-dimethyl-1-azaspiro[4.4]non-7-ene (5b). Compound **5b** was obtained similarly to **5a**, from **3b** (0.38 g, 2.0 mmol) and acyl chloride **4** (0.64 g, 2.3 mmol) in CH_2Cl_2 (8 mL) upon alkalination with 20% aq. NaOH (0.8 mL, 5.0 mmol). After work-up and concentration, a residual oil was heated with hexane for crystallization to obtain **5b** (0.70 g, 90%) as a white powder, m.p. 130—131 °C. *Due to the hindered rotation in the amide group, doubling, overlap, and broadening of some signals are observed in the NMR spectra.* ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.96 (s, 1 H, $(HC=)_{arom}$); 6.78 and 6.75 (both s, total 1 H, $(HC=)_{arom}$); 5.91 (s, 2 H, OCH_2O); 5.70 and 5.59 (both s, total 2 H, CH=); 3.68 and 3.45 (both s, total 2 H, $CH_2C=O$); 3.14 and 2.95 (both d, total 2 H, $C\underline{H}_2CH=$, J = 14.2 Hz and 15.3 Hz); 2.56 and 2.09 (both d, total 2 H, $C\underline{H}_2CH=$, J = 15.3 Hz and 14.2 Hz); 1.99 (t, 1 H, $C\underline{H}_aH_b$, J = 7.1 Hz); 1.92—1.82 (m, 2 H, CH_2); 1.76 (t, 1 H, $CH_a\underline{H}_b$, J = 7.1 Hz); 1.54 and 1.49 (both s, total 6 H, 2 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 169.32; 168.52; 147.22; 147.17; 147.13; 146.99; 129.57; 129.53; 129.09; 128.64; 115.11; 112.59; 111.72; 111.14; 101.61; 72.93; 69.21; 65.08; 61.46; 48.77; 45.02; 43.48; 42.85; 42.53; 41.37; 39.93; 39.10; 28.74; 26.54. MS (70 eV, EI): m/z 312 [M^+ − Br] (100); 260/258 (3); 242/240 (3); 215/213 (14); 179 (12); 178 (65); 136 (11); 107 (7); 91 (9); 77 (11). Found (%): C, 58.21; H, 5.69; N, 3.62; Br, 20.19. $C_{19}H_{22}NO_3Br$ (392.3). Calculated (%): C, 58.17; H, 5.65; N, 3.57; Br, 20.37.

[(6-Bromo-1,3-benzodioxol-5-yl)-acetyl]-6-azaspiro[4.5]-dec-2-ene (5c). Compound **5c** was obtained similarly to **5a**, from **3c** (0.50 g, 2.87 mmol) and acyl chloride **4** (1.10 g, 4.0 mmol) in CH_2Cl_2 (8 mL) upon alkalination with 20% aq. NaOH (2.6 mL, 16.0 mmol). After work-up and concentration, a residual oil was heated with hexane for crystallization to obtain **5c** (1.02 g, 94%) as a cream powder, m.p. 111—112 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.97 (s, 1 H, $(HC=)_{arom}$); 6.77 (s, 1 H, $(HC=)_{arom}$); 5.92 (s, 2 H, OCH_2O); 5.60 (s, 2 H, 2 CH=); 3.67 (s, 2 H, $CH_2C=O$); 3.45—3.42 (m, 2 H, CH_2N); 2.93 (d, 2 H, $C\underline{H}_2CH=$, J = 14.6 Hz); 2.36 (d, 2 H, $C\underline{H}_2CH=$, J = 14.6 Hz); 1.67—1.60 (m, 6 H, 3 CH_2). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 170.27; 147.36; 147.23; 128.82; 128.33 (2 C); 114.95; 112.54; 110.65; 101.67; 65.31; 44.03(2C); 43.49; 42.80; 34.43; 23.87; 17.41. MS (70 eV, EI): m/z 379/377 [M^+] (0.5); 299 (23); 298 [M^+ − Br] (100); 215 (14); 213 (13); 178 (15); 164 (12); 136 (10); 135 (10); 91 (18); 77 (11). Found (%): C, 57.12; H, 5.29; N, 3.76; Br, 21.27. $C_{18}H_{20}NO_3Br$ (378.3). Calculated (%): C, 57.15; H, 5.33; N, 3.70; Br, 21.12.

The Heck cyclization reaction. (1*S*,14*S*,17*R*)-14-(Hydroxymethyl)-5,7-dioxa-13-azapentacyclo[15.2.1.0^{2,10}.0^{4,8}.0^{13,17}]icosa-2(10),3,8,18-tetraen-12-one (6a) and (1*R*,14*S*,17*S*)-14-(hydroxymethyl)-5,7-dioxa-13-azapentacyclo[15.2.1.0^{2,10}.0^{4,8}.0^{13,17}]-icosa-2(10),3,8,18-tetraen-12-one (7a) (general procedure). Amide **5a** (0.39 g, 1.0 mmol), NaOAc (0.21 g, 2.6 mmol), [Pd] catalyst (46 mg, 0.05 mmol, 5 mol.%), and n-Bu_4NBr (0.1 g, 0.31 mmol) were placed into a Schlenk vessel, followed by addition of MeCN (5 mL), DMF (5 mL), and H_2O (1 mL) to this mixture of reagents. A suspension obtained was degassed by three cycles of freezing—evacuation—filling with argon. The degassed mixture was capped and heated at 125 °C for the time indicated in the corresponding Scheme. After the reaction reached completion, the mixture was filtered and concentrated at reduced pressure, the residue was diluted with water (30 mL) and extracted with EtOAc (3×8 mL). Combined extracts were dried with K_2CO_3 and concentrated at reduced pressure. The residue was purified by column chromatography, eluting with EtOAc to isolate isomers **6a** and **7a** in overall 82% yield.

Compound 6a. The yield was 0.152 g (48.5%), clear crystals, R_f = 0.23 (EtOAc); m.p. 204—205 °C, $[\alpha]_D^{25}$ +134.4 (c = 1; $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.71 (s, 1 H, $(HC=)_{arom}$); 6.60 (s, 1 H, $(HC=)_{arom}$); 6.05 (dd, 1 H, CH=, J = 2.9 Hz, J = 5.3 Hz); 5.88 (d, 1 H, $OC\underline{H}_aH_bO$, J = 1.4 Hz); 5.85 (d, 1 H, $OCH_a\underline{H}_bO$, J = 1.4 Hz); 5.82 (d, 1 H, CH=, J = 5.3 Hz); 4.92 (d, 1 H, $C\underline{H}_aH_bC=O$, J = 13.1 Hz); 4.40 (ddd, 1 H, CHN, J = 5.7 Hz, J = 7.5 Hz, J = 6.9 Hz); 4.00 (t, 1 H, OH, J = 4.8 Hz); 3.80 (dd, 1 H, $C\underline{H}Ar$, J = 1.7 Hz, J = 8.8 Hz); 3.66 (ddd, 1 H, $C\underline{H}_aH_bOH$, J = 3.5 Hz, J = 6.6 Hz, J = 10.6 Hz); 3.56 (dt, 1 H, $CH_a\underline{H}_bOH$, J = 5.2 Hz, J = 10.7 Hz); 3.12 (d, 1 H, $CH_a\underline{H}_bC=O$, J = 13.1 Hz); 2.33 (ddd, 1 H, $C\underline{H}_aH_bCHN$, J = 6.8 Hz, 12.6 Hz, 13.5 Hz); 2.27 (dd, 1 H, $C\underline{H}_aH_bCHAr$, J = 9.1 Hz, J = 13.4 Hz); 1.91 (dddd, 1 H, $CH_a\underline{H}_bCHN$, J = 6.5 Hz, J = 9.1 Hz, J = 13.2 Hz, J =15.3 Hz); 1.87 (d, 1 H, $CH_a\underline{H}_bCHAr$, J = 13.6 Hz); 1.79—1.72 (m, 2 H, CH_2C). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 174.55; 146.74; 146.27; 135.22; 134.82; 134.51; 127.71; 113.97; 110.14; 101.10; 75.86; 66.60; 60.70; 53.01; 49.56; 40.52; 39.50; 24.63. MS (70 eV, EI): m/z 313 [M^+] (22); 283 (19); 282 (100); 255 (11); 254 (72); 237 (12); 212 (21); 211 (64); 210 (11); 199 (16); 181 (21); 172 (30); 153 (17); 115 (10); 82 (11). Found (%): C, 69.07; H, 6.09; N, 4.48. $C_{18}H_{19}NO_4$ (313.3). Calculated (%): C, 68.99; H, 6.11; N, 4.47.

Compound 7a. The yield was 0.105 g (33.5%), oil, R_f = 0.31 (EtOAc); $[\alpha]_D^{25}$ −184.8 (c = 1; $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.71 (s, 1 H, $(HC=)_{arom}$); 6.61 (s, 1 H, $(HC=)_{arom}$); 6.08 (dd, 1 H, CH=, J = 3.0 Hz, J = 5.3 Hz); 5.90 (s, 1 H, $OC\underline{H}_aH_bO$); 5.88 (s, 1 H, $OCH_a\underline{H}_bO$); 5.78 (d, 1 H, CH=, J = 5.3 Hz); 5.04 (br.s, 1 H, OH); 5.01 (d, 1 H, $C\underline{H}_aH_bC=O$, J = 13.4 Hz); 4.37—4.29 (m, 1 H, CHN); 3.77 (dd, 1 H, CHAr, J = 2.5 Hz, J = 8.7 Hz); 3.60—3.54 (m, 2 H, $C\underline{H}_2OH$); 3.14 (d, 1 H, $CH_a\underline{H}_bC=O$, J = 13.2 Hz); 2.36 (dd, 1 H, $C\underline{H}_aH_bCHAr$, J = 8.9 Hz, J = 13.2 Hz); 2.23—2.13 (m, 1 H, $C\underline{H}_aH_bCHN$); 2.07—1.98 (m, 2 H, CH_2C); 1.94 (d, 1 H, $CH_a\underline{H}_bCHAr$, J = 13.2 Hz); 1.67—1.56 (m, 1 H, $CH_a\underline{H}_bCHN$). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 173.91; 146.86; 146.28; 134.47; 134.33; 134.05; 127.39; 113.97; 110.23; 101.12; 74.50; 67.29; 64.31; 52.76; 50.04; 41.18; 38.89; 26.66. Found (%): C, 68.85; H, 5.97; N, 4.43. $C_{18}H_{19}NO_4$ (313.3). Calculated (%): C, 68.99; H, 6.11; N, 4.47.

(1*S,17*R**)-14,14-Dimethyl-5,7-dioxa-13-azapentacyclo-[15.2.1.0^{2,10}.0^{4,8}.0^{13,17}]icosa-2(10),3,8,18-tetraen-12-one (6b).** The yield was 0.29 g (94%), m.p. 143—144 °C. R_f(**5b**) = 0.58 (n-hexane : EtOAc = 1 : 1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.71 (s, 1 H, $(HC=)_{arom}$); 6.58 (s, 1 H, $(HC=)_{arom}$); 5.97 (dd, 1 H, CH=, J = 3.0 Hz, J = 5.5 Hz); 5.87 (d, 1 H, $OC\underline{H}_aH_bO$, J = 1.6 Hz); 5.85 (d, 1 H, $OCH_a\underline{H}_bO$, J = 1.6 Hz); 5.78 (dd, 1 H, CH=, J = 0.9 Hz, J = 5.5 Hz); 4.94 (d, 1H, $C\underline{H}_aH_bC=O$, J = 13.3 Hz); 3.73 (dd, 1 H, CHAr, J = 2.7 Hz, J = 8.9 Hz); 3.03 (d, 1 H, $CH_a\underline{H}_bC=O$, J = 13.2 Hz); 2.31 (dd, 1 H, $C\underline{H}_aH_bCHAr$, J = 9.1 Hz, J = 13.5 Hz); 2.20 (dt, 1 H, $C\underline{H}_aH_bCHN$, J = 8.0 Hz, J = 12.6 Hz); 1.90—1.80 (m, 2 H, $CH_a\underline{H}_bCHN$ and $CH_a\underline{H}_bCHAr$); 1.76—1.71 (m, 2 H, CH_2C); 1.42 (s, 3 H, CH_3); 1.40 (s, 3 H,

CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 171.45; 146.49; 146.09; 135.80; 134.45; 133.34; 128.50; 114.05; 109.94; 100.97; 75.33; 64.19; 52.94; 50.58; 43.03; 39.31; 38.12; 26.48; 26.25. MS (70 eV, EI): *m/z* 311 [M^+] (100); 296 (14); 268 (27); 253 (27); 255 (22); 213 (20); 212 (40); 211 (28); 199 (28); 195 (20); 181 (18); 172 (18); 153 (16); 115 (17); 49 (10). Found (%): C, 73.28; H, 6.90; N, 4.46. $C_{19}H_{21}NO_3$ (311.4). Calculated (%): C, 73.29; H, 6.80; N, 4.50.

(1*S, 18*R**)-5,7-Dioxa-13-azapentacyclo[16.2.1.0^{2,10}.0^{4,8}.0^{13,18}]heneicosa-2(10),3,8,19-tetraen-12-one (6c).** The yield was 0.10 g (34%), white powder, m.p. 114.5—115.5 °C. R_f (**5c**) = = 0.40 (*n*-hexane : EtOAc = 1 : 1). ^1H NMR (300 MHz, $CDCl_3$), δ: 6.70 (s, 1 H, $(HC=)_{arom}$); 6.57 (s, 1 H, $(HC=)_{arom}$); 5.95 (d, 1 H, CH=, *J* = 4.8 Hz); 5.86—5.83 (m, 3 H, OCH_2O and CH=); 5.11 (br.s, 1 H, $C\underline{H}_aH_bC{=}O$); 4.19 (br.s, 1 H, CHAr); 3.80 (d, 1 H, $C\underline{H}_aH_bCHAr$, *J* = 8.7 Hz); 3.20 (br.s, 1 H, $CH_a\underline{H}_bC{=}O$); 2.89 (br.s, 1 H, $C\underline{H}_aH_bCHN$); 2.19 (dd, 1 H, $CH_a\underline{H}_bCHAr$, *J* = 9.1 Hz, *J* = 13.5 Hz); 1.85—1.54 (m, 7 H, $CH_a\underline{H}_bCHN$ and 3 CH_2). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 175.02; 146.73; 146.23; 137.18; 133.89; 131.61; 128.61; 114.10; 109.90; 100.99; 69.69; 53.11; 46.14; 42.22; 41.13; 38.33; 23.47; 19.28. MS (70 eV, EI): *m/z* 297 [M^+] (100); 268 (15); 227 (13); 214 (15); 213 (33); 200 (25); 199 (38); 190 (9); 185 (11); 183 (20); 178 (12); 177 (73); 173 (16); 169 (17); 155 (18); 153 (15); 141 (18); 115 (22); 97 (10); 77 (8). Found (%): C, 72.67; H, 6.39; N, 4.78. $C_{18}H_{19}NO_3$ (297.3). Calculated (%): C, 72.71; H, 6.44; N, 4.71.

2,2-Diallyl-1-[(6-bromo-1,3-benzodioxol-5-yl)acetyl]azetidine. Solid acyl chloride **4** (1.55 g, 5.6 mmol) was added in portions to a mixture of 2,2-diallylazetidine (0.71 g, 5.2 mmol) and 15% solution of NaOH (2.6 mL, 10 mmol) in CH_2Cl_2 (20 mL) with vigorous stirring at +10 °C (water bath). After the addition was completed, the mixture was stirred for 20 min (TLC monitoring, *n*-hexane : EtOAc = 1 : 1). After the reaction reached completion, powdered K_2CO_3 was added and the suspension was filtered through Celite, the filtrate was washed with 1 *M* aq. HCl, dried with Na_2SO_4, concentrated at reduced pressure, the residue was dried *in vacuo* to obtain the amide (1.85 g, 94%) as a yellow oil, R_f = 0.34 (*n*-hexane : EtOAc = 4 : 1). Some compound was recrystallized from *n*-hexane at −18 °C for elemental analysis, the crystals obtained melt back to an oil on heating. *Due to the hindered rotation in the amide group, doubling, overlap, and broadening of some signals are observed in the NMR spectra.* ^1H NMR (300 MHz, $CDCl_3$), δ: 6.96 (s, 1 H, $(HC=)_{arom}$); 6.87 and 6.84 (both s, total 1 H, $(HC=)_{arom}$); 5.92 (s, 2 H, OCH_2O); 5.90—5.78 (m, 2 H, 2 CH=); 5.20—5.10 (m, 4 H, $2CH_2=$); 3.85 and 3.70 (both t, total 2 H, CH_2N, *J* = 7.8 Hz); 3.49 and 3.37 (both s, total 2 H, $CH_2C{=}O$); 2.82 and 2.66 (both dd, total 2 H, CH_2 (in allyl), *J* = 6.6 Hz, *J* = 13.9 Hz, *J* = 6.4 Hz, *J* = 14.2 Hz); 2.41 and 2.33 (both dd, total 2 H, CH_2 (in allyl), *J* = 8.0 Hz, *J* = 14.4 Hz, *J* = 8.0 Hz, *J* = 13.9 Hz); 2.10 and 2.05 (both t, total 2 H, CH_2C, *J* = 8.0 Hz, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$), δ *the major rotamer*: 168.77; 147.41; 133.27; 127.69; 118.97; 114.72; 112.39; 111.25; 101.71; 71.02; 45.91; 41.52; 39.31; 22.76. MS (70 eV, EI): *m/z* 338/336 [$M^+ - C_3H_5$] (2); 299 (23); 298 [$M^+ - Br$] (100); 215/213 (30); 191 (12); 190 (99); 178 (10); 149 (9); 135 (11); 121 (16); 105 (8); 96 (44); 93 (15); 91 (16); 79 (22); 77 (19). Found (%): C, 57.24; H, 5.38; N, 3.69; Br, 21.17. $C_{18}H_{20}NO_3Br$ (378.3). Calculated (%): C, 57.15; H, 5.33; N, 3.70; Br, 21.12.

[(6-Bromo-1,3-benzodioxol-5-yl)acetyl]-1-azaspiro[3.4]-oct-6-ene (5d). A Grubbs catalyst [Ru] (28 mg, 0.034 mmol, 1.0 mol.%) was added in two equal portions (each after 30 min) to a degassed solution of 2,2-diallyl-1-[(6-bromo-1,3-benzodioxol-5-yl)acetyl]azetidine (1.30 g, 3.43 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was heated for ~1.5 h at 37—40 °C, monitoring the reaction progress by TLC, *n*-hexane : EtOAc = = 4 : 1, R_f (**5d**) = 0.13. After the reaction reached completion, the solvent was evaporated, the residue was dissolved in the *n*-hexane : EtOAc = 4 : 1 mixture, and the solution obtained was passed through the layer of silica gel (3.5×5 cm), then the product was eluted with the *n*-hexane : EtOAc = 3 : 1 mixture. The solvents were evaporated to obtain compound **5d** (1.09 g, 91%) as an oil. *Due to the hindered rotation in the amide group, doubling, overlap, and broadening of some signals are observed in the NMR spectra.* ^1H NMR (300 MHz, $CDCl_3$), δ: 6.96 and 6.95 (both s, total 1 H, $(HC=)_{arom}$); 6.85 and 6.78 (both s, total 1 H, $(HC=)_{arom}$); 5.92 (s, 2 H, OCH_2O); 5.71 and 5.63 (both s, total 2 H, 2 CH=); 4.08 and 3.90 (both t, total 2 H, CH_2N, *J* = 7.6 Hz); 2.41 and 3.37 (both s, total 2 H, $CH_2C{=}O$); 3.21 and 3.04 (both d, total 2 H, $C\underline{H}_2CH=$, *J* = 15.6 Hz, *J* = 16.8 Hz); 2.74 and 2.42 (both d, total 2 H, $C\underline{H}_2CH=$, *J* = 16.8 Hz, *J* = 15.6 Hz); 2.35 and 2.25 (both t, total 2 H, CH_2C, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 169.37; 168.48; 147.43; 147.04; 147.29; 147.23; 128.86; 128.31; 127.85; 115.12; 114.76; 112.48; 112.42; 111.12; 111.03; 101.70; 101.67; 73.48; 73.26; 47.19; 46.21; 43.89; 43.21; 40.08; 39.44; 33.21; 32.58. MS (70 eV, EI): *m/z* 351/349 [M^+] (0.1); 271 (17); 270 (92); 260/258 (3); 241 (14); 215/213 (42); 192 (17); 190 (100); 162 (12); 135 (14); 91 (18); 79 (17); 78 (16); 77 (20); 51 (4). Found (%): C, 54.69; H, 4.78; N, 4.05; Br, 22.67. $C_{16}H_{16}NO_3Br$ (350.2). Calculated (%): C, 54.87; H, 4.61; N, 4.00; Br, 22.82.

X-ray diffraction study of compound 6a. Crystals $C_{18}H_{19}NO_4$ (*M* = 313.34) are orthorhombic, the space group is $P2_12_12_1$, at *T* = 100.0(2) K, *a* = 8.3373(3) Å, *b* = 9.8045(5) Å, *c* = 17.9452(9) Å, *V* = 1466.90(12) Å^3, *Z* = 4, d_{calc} = 1.419 g cm^{-3}, F(000) = 664, μ = 0.100 mm^{-1}. Parameters of the unit cell and intensities of 19109 reflections (4230 independent reflections, R_{int} = 0.039) were measured on a Bruker SMART APEX II CCD automatic three-circle diffractometer (λMo*K*α-irradiation, a graphite monochromator, φ- and ω-scanning, 2θ = 60°). The structure was solved by the direct methods and refined by the full-matrix least squares method on F^2 in anisotropic approximation for nonhydrogen atoms. The hydrogen atom of the hydroxy group was localized objectively in the differential Fourier syntheses and refined in isotropic approximation with the fixed position and thermal parameters (U_{iso}(H) = 1.2U_{eq}(O)). Position of the rest of hydrogen atoms were calculated geometrically and refined in isotropic approximation with the fixed position (riding model) and thermal parameters (U_{iso}(H) = 1.2U_{eq}(C)). The final divergence factors are: R_1 = 0.035 for 3948 independent reflections with $I \geq 2\sigma(I)$ and wR_2 = 0.088 for all the independent reflections. The maximum and minimum values for the peaks of residual electron density are equal to 0.329 and −0.289 e Å^{-3}, respectively. All the calculations were performed using the SHELXTL program package.[11] Tables of atom coordinates, bond distances, bond and torsional angles, and anisotropic temperature parameters for compound **6a** were deposited with the Cambridge Structural Database (CCDC 679405).

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