Domino-*Heck* Reactions of Carba- and Oxabicyclic, Unsaturated Dicarboximides: Synthesis of Aryl-Substituted, Bridged Perhydroisoindole Derivatives

by **Cumali Celik**[a]), **Irem Kulu**[a]), **Nuket Ocal***[a]), and **Dieter E. Kaufmann***[b])

[a]) Yildiz Technical University, Faculty of Art and Sciences, Department of Chemistry, Davutpasa Campus, 34210 Istanbul, Turkey (phone: +90-212-3834214; e-mail: nocal@yildiz.edu.tr)
[b]) Clausthal University of Technology, Institute of Organic Chemistry, Leibnizstr. 6, D-38678 Clausthal-Zellerfeld

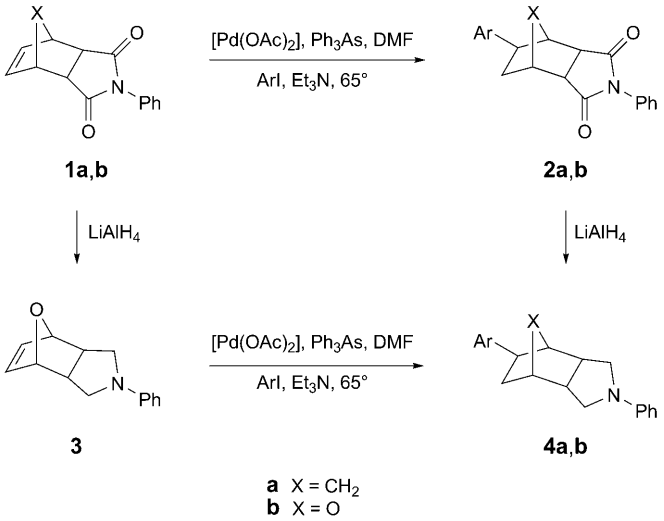
The C–C coupling of the two bicyclic, unsaturated dicarboximides **5** and **6** with aryl and heteroaryl halides gave, under reductive *Heck* conditions, the *C*-aryl-*N*-phenyl-substituted oxabicyclic imides **7a–c** and **8a–c** (*Scheme 3*). Domino-*Heck* C–C coupling reactions of **5**, **6**, and **1b** with aryl or heteroaryl iodides and phenyl- or (trimethylsilyl)acetylene also proved feasible giving **8**, **9**, and **10a–c**, respectively (*Scheme 4*). Reduction of **1b** with $LiAlH_4$ (→**11**) followed by *Heck* arylation and reduction of **5** with $NaBH_4$ (→**13**) followed by *Heck* arylation open a new access to the bridged perhydroisoindole derivatives **12a**,**b** and **14a**,**b** with prospective pharmaceutical activity (*Schemes 5* and *6*).

Introduction. – Due to its broad synthetic potential as a stereoselective C–C coupling method, the *Heck* reaction has been the subject of several synthetic and mechanistic studies over the last 30 years [1–5]. Originally developed to arylate acyclic alkenes, the reaction scope has been extended to cyclic compounds later, too. Rigid bi- and multicyclic systems make the catalytic oxidative *Heck*-coupling reaction impossible. To circumvent this problem, domino-*Heck* reactions were introduced with a hydroarylation reaction as its simplest variant [6–8], leading to a reductive C–C coupling reaction. *Kaufmann* and co-workers have been carrying out new examples of reductive *Heck* reactions using bicyclic systems aiming at the synthesis of new biologically active compounds [9–15].

In our previous works, we have accomplished Pd-catalyzed domino-*Heck* applications of bi- and tricyclic precursors of epibatidine analogs [16]. We then focused on reductive *Heck* reactions of polyfunctional tricyclic molecules with a strained C=C bond and an *N*-(acylamino)imide group [17].

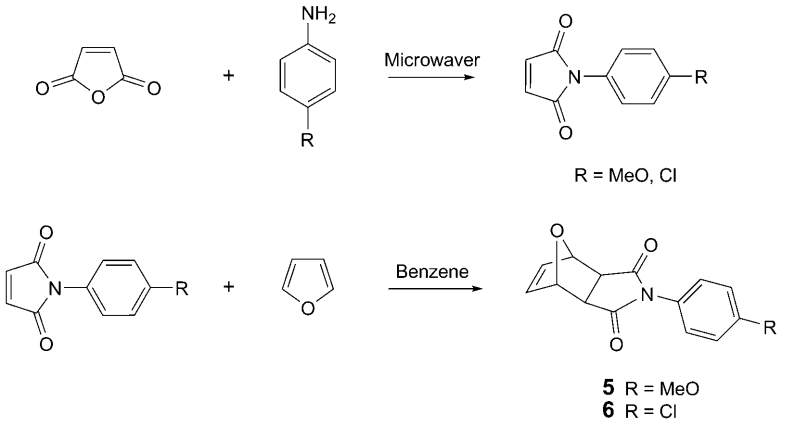
Later, we became interested in the synthesis of bioactive norcantharidin analogues **3** and **4b** that represent aryl-modified bicyclic imide systems, too. We had first synthesized *N*-phenylbicyclo[2.2.1]hept-5-ene-2-*endo*,3-*endo*-dicarboximide (**1a**) and *N*-phenyl-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-*exo*-dicarboximide (**1b**) as starting compounds according to [18][19]. We then investigated their hydroarylation reactions with aryl- and heteroaryl iodides (ArI) in the presence of Ph_3As giving **2a**,**b** and subsequent reduction reactions by $LiAlH_4$ to open a new access to perhydroisoindole derivatives **4a**,**b** [20] (*Scheme 1*). In reductive arylation reactions, Ph_3As has proved to be superior to Ph_3P and carbenes as ligands in both selectivity and yield [21].

Scheme 1



Results and Discussion. – We now have prepared *N*-(4-methoxyphenyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-*exo*-dicarboximide[1]) (**5**) and the 4-chlorophenyl derivative **6** as the starting compounds in good yields (70 and 72%, resp.) [22][23] (*Scheme 2*).

Scheme 2



Treatment of **5** with iodobenzene, 2-iodothiophene, and 2-chloro-5-iodopyridine under reductive *Heck* conditions gave the pure products **7a**–**c** after chromatographic separation on silica gel as single diastereoisomers in isolated yields of 48–75%

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

(*Scheme 3*). The configuration was inferred from their NMR spectra including diagnostic spin–spin interactions. The *exo*-position of the C(5)[1]) substituent was confirmed by the fact that H–C(5) showed no significant interaction with H–C(1). The geminal H-atoms at C(6) were identified by vicinal coupling to H–C(1). The *Table* shows selected ^{1}H-NMR data of the hydroarylation products **7a–c**.

Scheme 3

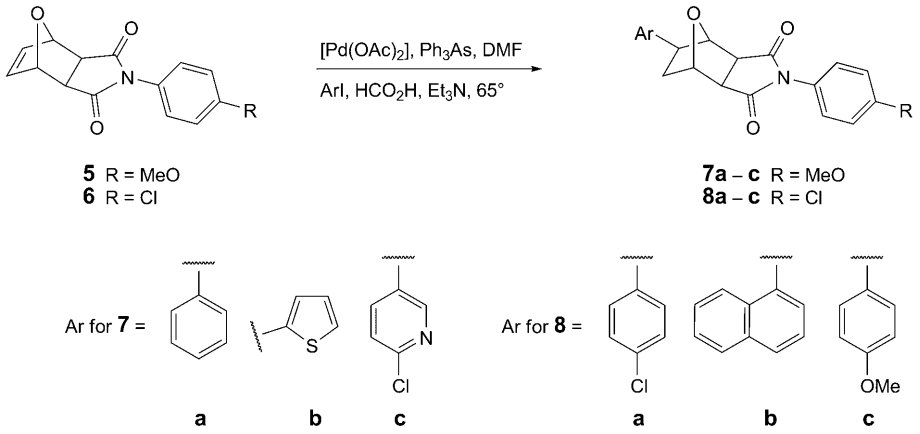
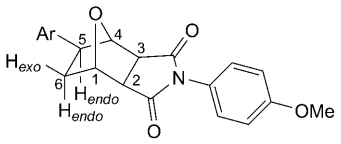


Table. *Selected ^{1}H-NMR Data* (δ in ppm) *of Compounds* **7a–c**[1])



7a – c

	7a	**7b**	**7c**
H–C(2)	3.13 (*d*)	3.11 (*d*)	3.15 (*d*)
H–C(3)	3.17 (*d*)	3.18 (*d*)	3.20 (*d*)
H–C(1)	5.13 (*d*)	5.14 (*d*)	5.16 (*d*)
H–C(4)	4.90 (*s*)	4.91 (*s*)	4.85 (*s*)

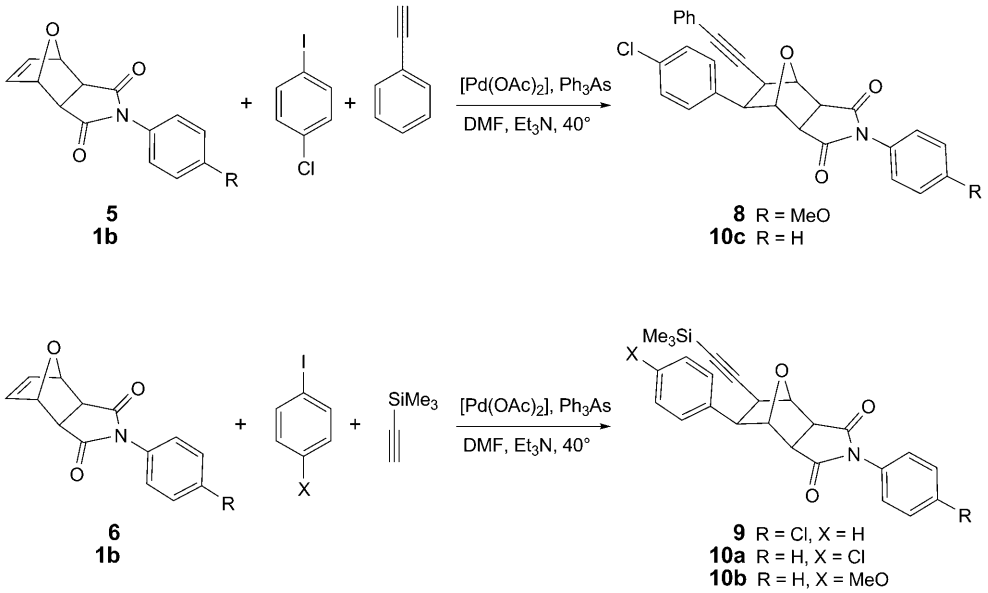
The same reductive *Heck*-arylation conditions were successfully applied to the reaction of **6** with 4-chloro-1-iodobenzene, 1-iodonaphthalene, and 1-iodo-4-methoxybenzene to give the new *exo*-arylated heterocycles **8a–c** in good yields after chromatographic separation (*Scheme 3*). Again, a characteristic coupling pattern between the bridgehead protons and H–C(5) and H–C(6) appeared in the ^{1}H-NMR spectra. Additionally, ^{1}H,^{1}H-COSY plots showed cross-peaks between H–C(2) and H–C(3) and between H–C(5) and H–C(6), respectively.

Research in the field of domino reactions is attracting considerable attention in synthetic organic chemistry since it enables the rapid assembly of complex molecules in one-pot processes [24]. Very elegant examples of Pd-catalyzed cascade processes

where a single catalytic cycle entails several sequential bond transformations have recently been reported [25][26]. In this work, we also would like to describe our results in the investigations on the Pd-catalyzed domino-*Heck*-type reactions of **5**, **6**, and **1b** [20].

The use of phenylacetylene or (trimethylsilyl)acetylene under domino-*Heck* conditions [16][17] provided alkynyl-substituted tricyclic imides **8**, **9**, and **10a–c** (*Scheme 4*). The structures were assigned by their ^{1}H,^{1}H-COSY and HSQC data.

Scheme 4

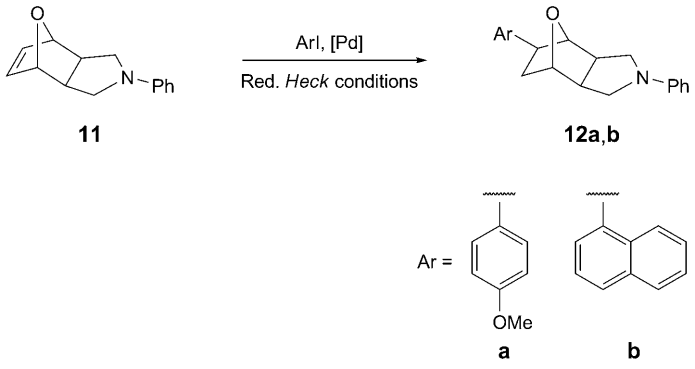


In addition to the ^{13}C-NMR and IR spectral data which were in agreement with the proposed structures, the mass spectra of all new compounds showed the expected molecular-ion peaks.

The structurally related perhydroisoindoles are selective sigma receptor antagonists and have a low potential for movement-disorder side effects associated with typical antipsychotic agents [27][28]. Therefore, we have first reduced *N*-phenyl-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*,3-*exo*-dicarboximide (**1b**) with $LiAlH_4$ to obtain **11**, followed by the synthesis of some perhydroisoindoles [20]. As part of our continuing interest in new perhydroisoindole derivatives, we now prepared **12a** and **12b** from **11** by the same *Heck*-arylation procedure (*Scheme 5*).

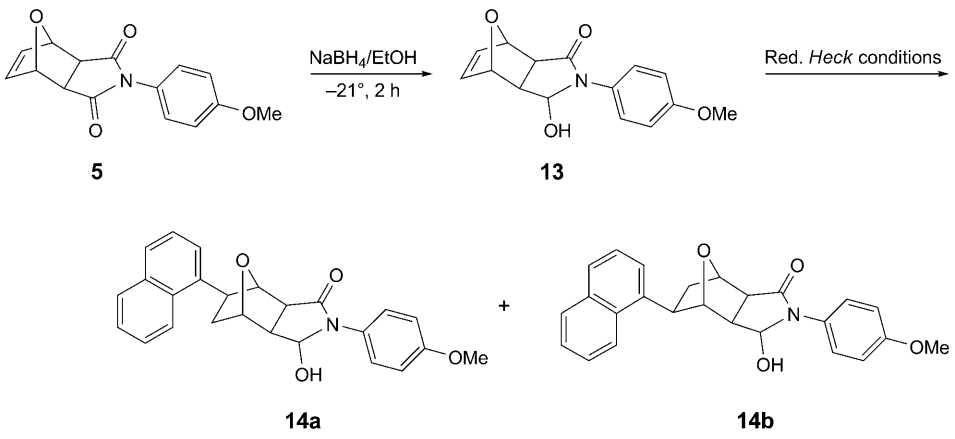
We also tried to reduce compound **5** with an excess of $LiAlH_4$ in Et_2O at temperatures ranging from 25 to $-40°$. After regular workup, the crude product was purified by column chromatography to obtain exclusively 1-(4-methoxyphenyl)-1*H*-pyrrole as the unexpected main product. Therefore, we subsequently reduced **5** with $NaBH_4$ in EtOH at $-21°$. Regular workup (HCl; column chromatography) gave compound **13** in 84% yield; its spectroscopic data and crystal structure have recently been reported [29]. Reductive arylation of **13** with 1-iodonaphthalene under *Heck*

Scheme 5



conditions gave the pure regioisomers **14a** and **14b** after column chromatography in yields of 50 and 37%, respectively (*Scheme 6*). The configuration of the new compounds was inferred from their ^{1}H-NMR and ^{1}H,^{1}H-COSY data. First evidence for the detection of both regioisomers was the observation that H–C(7) at δ 4.88 appeared as a *d* in the ^{1}H-NMR spectrum of **14a**, while it appeared as a *s* at δ 4.89 for **14b**. In the ^{1}H,^{1}H-COSY plot of **14a**, interaction between H_{exo}–C(8) and H–C(7) was clearly seen, but the spectrum of **14b** did not show the same coupling due to the 8_{exo}-substituent. The HSQC and MS data were also in agreement with the proposed structures.

Scheme 6



Conclusions. – In the presence of Ph_3As as a ligand, the Pd-catalyzed hydroarylation of the easily accessible tricyclic *N*-phenyl derivatives of the unsaturated imides **5** and **6** was proven to be a stereoselective, versatile, and high-yield approach to the synthesis of aryl and heteroaryl derivatives of heterotricyclic systems. Domino-

Heck C–C coupling reactions with aryl or heteroaryl halides were shown to be feasible in the presence of (trimethylsilyl)acetylene or phenylacetylene. Our results also demonstrated that the reductive access to aryl-substituted bridged perhydroisoindole derivatives will be useful for the construction of novel heterocycles of potential pharmacological interest.

We gratefully acknowledge financial support of this work by the *Yildiz Technical University Scientific Research Projects Coordination Department* (Project No. 26-01-02-04).

Experimental Part

General. All reactions were conducted under N_2 and carried out in a *Schlenk* system. M.p.: *Gallenkamp*-melting-point apparatus; uncorrected. Column chromatography (CC): silica gel (SiO_2) *60*. TLC: SiO_2-precoated (0.2 mm layer) Al sheets (*Merck*). IR Spectra: *Perkin-Elmer* FT-IR spectrometer; KBr pellets; in cm^{-1}. NMR Spectra: *Bruker-Digital-FT-NMR-Avance* (400 MHz) and *Varian Inova* (500 MHz) spectrometers; $CDCl_3$ solns.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Varian-Saturn-2100T*/*GC3900* GC/MS spectrometer; FAB ionization; in *m*/*z*. Elemental analyses: *Thermo-Flash-EA-1112* elemental analyzer for C, H, N, and S.

Reductive Heck *Reactions of* **5** *and* **6**: *General Procedure.* A soln. of $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol) and Ph_3As (33.7 mg, 0.11 mmol) in anh. DMF or DMSO (3 ml) was stirred under N_2 at 65° for 15 min. Then, **5** (271 mg, 1 mmol) or **6** (275.5 mg, 1 mmol), Et_3N (488 µl, 3.5 mmol), the appropriate aryl or heteroaryl iodide (1.5 mmol), and HCOOH (138 mg, 3 mmol) were added. The mixture was stirred for 8–24 h. After cooling to r.t., AcOEt and brine were added. The org. layer was dried ($MgSO_4$), the solvent evaporated, and the residue purified by CC.

N-*(4-Methoxyphenyl)-5*-exo-*phenyl-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*7*R,*7a*S*)-Hexahydro-2-(4-methoxyphenyl)-5-phenyl-4,7-epoxy-1*H-*isoindole-1,3(2*H*)-dione*; **7a**). CC (AcOEt/hexane 3:2): **7a** (63%). Colorless crystals. M.p. 241°. IR: 3085, 3012, 2922, 1709, 1605, 1512, 1437, 1396, 1254, 1198, 1024, 880, 772, 737. ^{1}H-NMR (400 MHz): 1.99–2.04 (*m*, H_{exo}–C(6)); 2.28 (*dd*, *J* = 8.97, 3.91, H_{endo}–C(6)); 3.07 (*dd*, *J* = 4.88, 3.91, H_{endo}–C(5)); 3.13 (*d*, *J* = 7.02, H–C(2)); 3.17 (*d*, *J* = 7.02, H–C(3)); 3.81 (*s*, MeO); 4.90 (*s*, H–C(4)); 5.13 (*d*, *J* = 4.86, H–C(1)); 6.96 (*d*, *J* = 9.28, 2 arom. H); 7.17 (*d*, *J* = 8.79, 2 arom. H); 7.23–7.32 (*m*, 5 arom. H). ^{13}C-NMR (100 MHz): 40.3; 47.7; 50.0; 50.4; 55.7; 79.8; 85.5; 114.8; 124.6; 127.1; 127.3; 127.9; 128.9; 144.2; 159.9; 176.3; 176.6. MS: 349 ($M^{+\cdot}$), 320, 203, 188, 134, 106, 91, 78. Anal. calc. for $C_{21}H_{19}NO_4$ (349.38): C 72.19, H 5.48, N 4.01; found: C 72.23, H 5.47, N 3.99.

N-*(4-Methoxyphenyl)-5*-exo-*(2-thienyl)-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*R,*5*S,*7*R,*7a*S*)-Hexahydro-2-(4-methoxyphenyl)-5-(2-thienyl)-4,7-epoxy-1*H-*isoindole-1,3(2*H*)-dione*; **7b**). CC (AcOEt/hexane 1:1): **7b** (48%). Colorless crystals. M.p. 181°. IR: 3073, 3011, 2925, 1706, 1606, 1589, 1482, 1437, 1394, 1254, 1195, 1025, 827, 709, 693. ^{1}H-NMR: 2.04–2.12 (*m*, H_{exo}–C(6)); 2.29 (*dd*, *J* = 8.97, 3.91, H_{endo}–C(6)); 3.11 (*d*, *J* = 7.02, H–C(2)); 3.18 (*d*, *J* = 7.02, H–C(3)); 3.44 (*dd*, *J* = 4.88, 3.91, H_{endo}–C(5)); 3.82 (*s*, MeO); 4.91 (*s*, H–C(4)); 5.14 (*d*, *J* = 4.86, H–C(1)); 6.84–6.88 (*m*, 1 arom. H); 6.92–6.99 (*m*, 3 arom. H); 7.15–7.18 (*m*, 3 arom. H). ^{13}C-NMR: 40.78; 43.21; 49.66; 49.76; 55.71; 79.7; 85.6; 114.8; 124.2; 124.4; 124.6; 127.0; 127.9; 147.3; 159.9; 176.4; 176.2. MS: 355 ($M^{+\cdot}$), 327, 203, 188, 162, 149, 134, 106, 92. Anal. calc. for $C_{19}H_{17}NO_4S$ (355.41): C 64.21, H 4.82, N 3.94, S 9.02; found: C 64.22, H 4.81, N 3.90, S 8.99.

5-exo-*(6-Chloropyridin-3-yl)*-N-*(4-methoxyphenyl)-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*7*R,*7a*S*)-5-(6-Chloropyridin-3-yl)hexahydro-2-(4-methoxyphenyl)-4,7-epoxy-1*H-*isoindole-1,3(2*H*)-dione*; **7c**). CC (AcOEt/hexane 3:2): **7c** (75%). Colorless crystals. M.p. 192°. IR: 3010, 2973, 2840, 1708, 1608, 1584, 1564, 1457, 1444, 1392, 1252, 1192, 1106, 827. ^{1}H-NMR (400 MHz): 1.88–1.94 (*m*, H_{exo}–C(6)); 2.33 (*dd*, *J* = 8.97, 3.91, H_{endo}–C(6)); 3.10 (*dd*, *J* = 4.88, 3.91, H_{endo}–C(5)); 3.15 (*d*, *J* = 7.02, H–C(2)); 3.20 (*d*, *J* = 7.02, H–C(3)); 3.81 (*s*, MeO); 4.85 (*s*, H–C(4)); 5.16 (*d*, *J* = 4.86, H–C(1)); 6.97 (*d*, *J* = 9.20, 2 arom. H); 7.16 (*d*, *J* = 8.80, 2 arom. H); 7.28 (*d*, *J* = 8.79, 1 arom. H); 7.62 (*dd*, *J* = 2.40, 6.00, 1 arom. H); 8.27 (*d*, *J* = 2.40, 1 arom. H). ^{13}C-NMR (100 MHz): 40.1;

44.1; 49.5; 49.8; 55.5; 79.4; 84.7; 114.5; 124.1; 124.5; 127.6; 137.3; 138.5; 148.5; 150.2; 159.7; 175.7; 176.0. MS: 382 ($M^{+\cdot}$), 354, 179, 150, 135, 106, 91. Anal. calc. for $C_{20}H_{17}ClN_2O_4$ (384.81): C 62.42, H 4.45, N 7.28; found: C 62.56, H 4.46, N 7.29.

N,5-exo-*Bis(4-chlorophenyl)-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*7*R,*7a*S*)-2,5-Bis(4-chlorophenyl)hexahydro-4,7-epoxy-1*H-*isoindole-1,3(2*H*)-dione*; **8a**). CC (AcOEt/hexane 3:2): **8a** (46%). Colorless crystals. M.p. 219°. IR: 3091, 3001, 2959, 1702, 1494, 1409, 1377, 1180, 1095, 824, 810. ^{1}H-NMR (400 MHz): 1.92–1.98 (*m*, H_{exo}–C(6)); 2.29 (*dd*, *J* = 8.97, 3.91, H_{endo}–C(6)); 3.05 (*dd*, *J* = 4.88, 3.91, H_{endo}–C(5)); 3.17 (*dd*, *J* = 7.02, 12.48, H–C(2), H–C(3)); 4.86 (*s*, H–C(4)); 5.13 (*d*, *J* = 4.86, H–C(1)); 7.18–7.29 (*m*, 6 arom. H); 7.43 (*d*, *J* = 8.58, 2 arom. H). ^{13}C-NMR (125 MHz): 39.1; 45.8; 48.7; 49.1; 78.6; 84.1; 126.7; 127.5; 127.8; 128.4; 129.2; 131.8; 141.4; 174.4, 174.7. MS: 387 ($M^{+\cdot}$), 359, 207, 178, 153, 90. Anal. calc. for $C_{20}H_{15}Cl_2NO_3$ (388.24): C 61.87, H 3.89, N 3.61; found: C 61.87, H 3.90, N 3.63.

N-*(4-Chlorophenyl)-5*-exo-*(naphthalen-1-yl)-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*7*R,*7a*S*)-2-(4-Chlorophenyl)hexahydro-5-(naphthalen-1-yl)-4,7-epoxy-1*H-*isoindole-1,3(2*H*)-dione*; **8b**). CC (AcOEt/hexane 3:2): **8b** (56%). Colorless crystals. M.p. 228°. IR: 3083, 3031, 2990, 2945, 1703, 1598, 1492, 1382, 1202, 1182, 1093, 828 802, 778. ^{1}H-NMR (400 MHz): 2.01–2.07 (*m*, H_{exo}–C(6)); 2.46 (*dd*, *J* = 8.97, 3.91, H_{endo}–C(6)); 3.27 (*d*, *J* = 7.02, H–C(2)); 3.35 (*d*, *J* = 7.02, H–C(3)); 3.88 (*dd*, *J* = 4.88, 3.91, H_{endo}–C(5)); 5.17 (*d*, *J* = 4.86, H–C(1)); 5.22 (*s*, H–C(4)); 7.22–7.27 (*m*, 1 arom. H); 7.44–7.58 (*m*, 7 arom. H); 7.75 (*d*, *J* = 8.70, 1 arom. H); 7.89 (*d*, *J* = 9.36, 1 arom. H); 8.01 (*d*, *J* = 8.19, 1 arom. H). ^{13}C-NMR (100 MHz): 39.9; 42.4; 49.3; 50.5; 80.1; 84.3; 122.9; 123.1; 125.9; 126.0; 126.5; 127.6; 128.0; 129.4; 129.6; 130.5; 131.3; 134.3; 134.9; 139.4; 175.8; 176.1. MS: 403 ($M^{+\cdot}$), 375, 207, 193, 179, 153, 90. Anal. calc. for $C_{24}H_{18}ClNO_3$ (403.86): C 71.38, H 4.49, N 3.47; found: C 71.27, H 4.38, N 3.45.

N-*(4-Chlorophenyl)-5*-exo-*(4-methoxyphenyl)-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*7*R,*7a*S*)-2-(4-Chlorophenyl)hexahydro-5-(4-methoxyphenyl)-4,7-epoxy-1*H-*isoindole-1,3(2*H*)-dione*; **8c**). CC (AcOEt/hexane 3:2): **8c** (59%). Colorless crystals. M.p. 169°. IR: 3097, 3072, 2989, 2836, 1704, 1611, 1582, 1513, 1495, 1406, 1380, 1254, 1176, 1092, 832, 812. ^{1}H-NMR (400 MHz): 1.95–2.01 (*m*, H_{exo}–C(6)); 2.27 (*dd*, *J* = 8.97, 3.91, H_{endo}–C(6)); 3.04 (*dd*, *J* = 4.88, 3.91, H_{endo}–C(5)); 3.14 (*d*, *J* = 7.02, H–C(2)); 3.19 (*d*, *J* = 7.02, H–C(3)); 3.79 (*s*, MeO); 4.86 (*s*, H–C(4)); 5.12 (*d*, *J* = 4.86, H–C(1)); 6.84 (*d*, *J* = 8.58, 2 arom. H); 7.18 (*d*, *J* = 8.58, 2 arom. H); 7.23 (*d*, *J* = 8.58, 2 arom. H); 7.43 (*d*, *J* = 8.58, 2 arom. H). ^{13}C-NMR (100 MHz): 40.4; 46.9; 50.0; 50.4; 55.5; 79.8; 85.7; 114.3; 127.9; 128.3; 129.6; 130.5; 134.8; 136.4; 158.8; 175.8; 176.1. MS: 383 ($M^{+\cdot}$), 290, 207, 147, 153, 91, 77. Anal. calc. for $C_{21}H_{18}ClNO_4$ (383.82): C 65.71, H 4.73, N 3.65; found: C 65.70, H 4.73, N 3.62.

Domino-Heck *Reactions of* **5**, **6**, *and* **1b**: *General Procedure.* A soln. of [Pd(OAc)$_2$] (5.6 mg, 25 µmol) and Ph_3As (55 µmol) in anh. DMF (3 ml) was stirred at 40° for 15 min. Then, **5** (or **6** or **1b)** (1 mmol), the aryl compound (1.5 mmol), Et_3N (488 µl, 3.50 mmol), and (trimethylsilyl)acetylene or phenylacetylene (3 mmol) were rapidly added in one portion. The mixture was kept at 40° for 24 h. After cooling to r.t., brine (50 ml) was added, the mixture extracted with AcOEt and dried ($MgSO_4$), the solvent evaporated, and the residue purified by CC.

5-(4-Chlorophenyl)-N-*(4-methoxyphenyl)-6*-exo-*(phenylethynyl)-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*6*S,*7*R,*7a*S*)-5-(4-Chlorophenyl)hexahydro-2-(4-methoxyphenyl-6-(2-phenylethynyl)-4,7-epoxy-1*H-*isoindole-1,3(2*H*)-dione*; **8**). CC (AcOEt/hexane 3:1): **8** (47%). Colorless crystals. M.p. 243°. IR: 3046, 3011, 2993, 2838, 1778, 1708, 1608, 1512, 1491, 1442, 1396, 1251, 1191, 1035, 756, 692, 677. ^{1}H-NMR (400 MHz): 3.26 (*d*, *J* = 7.02, H–C(2)); 3.29 (*d*, *J* = 7.02, H–C(3)); 3.43 (*d*, *J* = 8.80, H_{endo}–C(6)); 3.54 (*d*, *J* = 8.80, H_{endo}–C(5)); 3.86 (*s*, MeO); 5.13 (*s*, H–C(4)); 5.20 (*s*, H–C(1)); 6.96–7.03 (*m*, 4 arom. H); 7.21–7.27 (*m*, 5 arom. H); 7.35 (*s*, 4 arom. H). ^{13}C-NMR (100 MHz): 42.8; 49.3; 49.6; 52.1; 55.6; 84.5; 85.0; 86.9; 87.0; 114.6; 122.6; 124.2; 127.7; 128.1; 128.2; 128.2; 130.2; 131.3; 133.0; 135.9; 138.2; 159.8; 175.5; 175.6. MS: 483 ($M^{+\cdot}$), 279, 203, 188, 150, 135, 106, 90. Anal. calc. for $C_{29}H_{22}ClNO_4$ (483.94): C 71.97, H 4.58, N 2.89; found: C 61.87, H 3.90, N 3.63.

N-*(4-Chlorophenyl)-5*-exo-*phenyl-6*-exo-*[2-(trimethylsilyl)ethynyl]-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*6*S,*7*R,*7a*S*)-2-(4-Chlorophenyl)hexahydro-5-phenyl-6-[2-(trimethylsilyl)ethynyl]-4,7-epoxy-1*H-*isoindole-1,3(2*H*)-dione*; **9**). CC (AcOEt/hexane 3:1): **9** (46%). Colorless crystals. M.p. 155°. IR: 3066, 3029, 2960, 2898, 2165, 1773, 1708, 1603, 1493, 1456, 1392, 1249, 1192, 1092, 757, 729, 699. ^{1}H-NMR (400 MHz): 0.08 (*s*, 3 Me); 3.24 (*s*, H–C(2), H–C(3)); 3.33 (*d*, *J* =

8.91, H_{endo}–C(6)); 3.37 (*d*, *J* = 8.91, H_{endo}–C(5)); 5.14 (*d*, *J* = 2.80, H–C(1), H–C(4)); 7.26–7.33 (*m*, 7 arom. H); 7.41 (*d*, *J* = 8.80, 2 arom. H). ^{13}C-NMR (100 MHz): –0.5; 43.0; 49.4; 49.7; 52.4; 84.6; 85.2; 91.4; 103.1; 127.1; 127.7; 128.0; 128.9; 129.5; 130.1; 134.8; 139.3; 175.1; 175.2. MS: 399, 242, 179, 153, 91, 74.

5-exo-*(4-Chlorophenyl)*-N-*phenyl*-exo-*[2-(6-trimethylsilyl)ethynyl]-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*6*S,*7*R,*7a*S*)-5-(4-Chlorophenyl)hexahydro-2-phenyl-6-[2-(trimethylsilyl)ethynyl]-4,7-epoxy-1*H*-isoindole-1,3(2*H*)-dione*; **10a**). CC (AcOEt/hexane 1:3): **10a** (56%). Colorless crystals. M.p. 226°. IR: 3034, 3015, 2961, 2900, 2161, 1781, 1705, 1598, 1495, 1457, 1393, 1248, 1188, 843, 738, 705. ^{1}H-NMR (500 MHz): 0.00 (*s*, 3 Me); 3.28 (*s*, H–C(2), H–C(3)); 3.37 (*d*, *J* = 8.91, H_{endo}–C(6)); 3.39 (*d*, *J* = 8.91, H_{endo}–C(5)); 5.15 (*s*, H–C(4)); 5.18 (*s*, H–C(1)); 7.31–7.36 (*m*, 5 arom. H); 7.49 (*d*, *J* = 8.80, 2 arom. H) 7.55 (*d*, *J* = 8.80, 2 arom. H). ^{13}C-NMR (125 MHz): 1.4; 45.0; 51.3; 51.6; 53.8; 86.5; 86.9; 93.8; 104.7; 129.9; 130.9; 131.1; 131.2; 132.2; 133.8; 134.9; 139.9; 177.0; 177.2. MS: 449 ($M^{+\cdot}$), 413, 242, 179, 153, 91, 74.

5-exo-*(4-Methoxyphenyl)*-N-*phenyl-6*-exo-*[2-(trimethylsilyl)ethynyl]-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*6*S,*7*R,*7a*S*)-Hexahydro-5-(4-methoxyphenyl)-2-phenyl-6-[2-(trimethylsilyl)ethynyl]-4,7-epoxy-1*H*-isoindole-1,3(2*H*)-dione*; **10b**). CC (AcOEt/hexane 1:1): **10b** (43%). Colorless crystals. M.p. 176°. IR: 3000, 2996, 2958, 2835, 2185, 1778, 1712, 1613, 1513, 1497, 1458, 1387, 1248, 1196, 1179, 845, 710, 695. ^{1}H-NMR (500 MHz): 0.00 (*s*, 3 Me); 3.26 (*s*, H–C(2), H–C(3)); 3.35 (*d*, *J* = 8.80, H_{endo}–C(6)); 3.39 (*d*, *J* = 8.80, H_{endo}–C(5)); 3.88 (*s*, MeO); 5.14 (*s*, H–C(4)); 5.17 (*s*, H–C(1)); 6.90–6.93 (*m*, 2 arom. H); 7.30–7.36 (*m*, 3 arom. H); 7.47–7.57 (*m*, 4 arom. H). ^{13}C-NMR (125 MHz): 0.0; 43.6; 49.8; 50.2; 52.2; 55.7; 85.0; 85.8; 91.7; 103.9; 113.8; 126.9; 129.3; 129.7; 130.4; 132.1; 132.2; 159.2; 175.8; 175.9. MS: 445 ($M^{+\cdot}$), 430, 414, 242, 179, 153, 91, 74.

5-exo-*(4-Chlorophenyl)*-N-*phenyl-6*-exo-*(2-phenylethynyl)-7-oxabicyclo[2.2.1]heptane-2*-exo,*3*-exo-*dicarboximide* (= rel-*(3a*R,*4*S,*5*R,*6*S,*7*R,*7a*S*)-5-(4-Chlorophenyl)hexahydro-2-phenyl-6-(2-phenylethynyl)-4,7-epoxy-1*H*-isoindole-1,3(2*H*)-dione*; **10c**). CC (AcOEt/hexane 1:3): **10c** (48%). Colorless crystals. M.p. 254°. IR: 3048, 3018, 2981, 2915, 2835, 2185, 1777, 1703, 1597, 1491, 1456, 1389, 1185, 791, 755, 743. ^{1}H-NMR (500 MHz): 3.25 (*d*, *J* = 7.32, H–C(2)); 3.27 (*d*, *J* = 7.32, H–C(3)); 3.41 (*d*, *J* = 8.80, H_{endo}–C(6)); 3.50 (*d*, *J* = 8.80, H_{endo}–C(5)); 5.11 (*s*, H–C(4)); 5.17 (*s*, H–C(1)); 6.92–6.95 (*m*, 2 arom. H); 7.17–7.28 (*m*, 8 arom. H); 7.39–7.49 (*m*, 4 arom. H). ^{13}C-NMR (125 MHz): 43.1; 49.6; 49.9; 52.3; 84.8; 85.2; 87.0; 87.3; 122.9; 126.7; 128.3; 128.3; 128.4; 129.2; 129.5; 130.4; 131.5; 131.8; 133.3; 138.4; 175.4; 175.5. MS: 453 ($M^{+\cdot}$), 438, 422, 279, 188, 135, 106, 51. Anal. calc. for $C_{28}H_{20}ClNO_3$ (453.92): C 74.09, H 4.44, N 3.09; found: C 73.97, H 4.49, N 3.01.

8-'exo'-*(4-Methoxyphenyl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decane* (= rel-*(3a*R,*4*R,*5*S,*7*S,*7a*S*)-Octahydro-5-(4-methoxyphenyl)-2-phenyl-4,7-epoxy-1*H*-isoindole*; **12a**). CC (AcOEt/hexane 1:3): **12a** (48%). Colorless crystals. M.p. 167°. IR: 3052, 2999, 2978, 2967, 2886, 2829, 1596, 1507, 1470, 1370, 1246, 1175, 1031, 829, 752, 693. ^{1}H-NMR (500 MHz): 1.75 (*ddd*, *J* = 12.20, 10.25, 4.88, H–C(9)); 2.08 (*dd*, *J* = 8.78, 12.20, H–C(9)); 2.67–2.74 (*m*, H–C(2), H–C(6)); 2.85–2.98 (*m*, 1 CH_2N, H–C(8)); 3.66–3.72 (*m*, 1 CH_2N); 3.77 (*s*, MeO); 4.26 (*s*, H–C(7)); 4.52 (*d*, *J* = 5.36, H–C(1)); 6.62 (*d*, *J* = 8.79, 2 arom. H); 6.70 (*d*, *J* = 7.32, 1 arom. H); 6.81 (*d*, *J* = 8.79, 2 arom. H); 7.18–7.23 (*m*, 4 arom. H). ^{13}C-NMR (125 MHz): 40.4; 46.9; 47.9; 48.4; 53.6; 53.8; 55.3; 80.8; 87.2; 113.6; 113.9; 116.9; 128.2; 129.0; 138.3; 148.4; 158.1. MS: 321 ($M^{+\cdot}$), 306, 244, 214, 138, 106, 77. Anal. calc. for $C_{21}H_{23}NO_2$ (321.41): C 78.47, H 7.21, N 4.36; found: C 78.54, H 7.16, N 4.38.

8-'exo'-*(Naphthalen-1-yl)-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decane* (= rel-*(3a*R,*4*R,*5*S,*7*S,*7a*S*)-Octahydro-5-(naphthalen-1-yl)-2-phenyl-4,7-epoxy-1*H*-isoindole*; **12b**). CC (AcOEt/hexane 1:8): **12b** (54%). Colorless crystals. M.p. 211°. IR: 3041, 2982, 2952, 2899, 2815, 1596, 1504, 1475, 1365, 1332, 1214, 1174, 786, 755, 693. ^{1}H-NMR (500 MHz): 1.85 (*ddd*, *J* = 12.20, 10.25, 4.88, H–C(9)); 2.27 (*dd*, *J* = 8.78, 12.20, H–C(9)); 2.81–2.92 (*m*, H–C(2), H–C(6)); 2.99–3.03 (*m*, CH_2N); 3.70–3.78 (*m*, CH_2N, H–C(8)); 4.58 (*d*, *J* = 5.36, H–C(1)); 4.61 (*s*, H–C(7)); 6.65 (*d*, *J* = 7.80, 2 arom. H); 6.73 (*d*, *J* = 7.32, 1 arom. H); 7.23 (*d*, *J* = 7.30, 2 arom. H); 7.42–7.54 (*m*, 3 arom. H); 7.58 (*d*, *J* = 6.84, 1 arom. H); 7.71 (*d*, *J* = 8.30, 1 arom. H); 7.85 (*d*, *J* = 7.80, 1 arom. H); 8.07 (*d*, *J* = 8.30, 1 arom. H). ^{13}C-NMR (125 MHz): 39.5; 42.0; 48.2; 48.6; 53.7; 53.8; 55.3; 81.1; 85.7; 113.6; 116.9; 123.0; 123.1; 125.4; 125.9; 126.6; 129.0; 129.1; 131.4; 133.9; 141.1. 148.4. MS: 341 ($M^{+\cdot}$), 214, 152, 97, 77. Anal. calc. for $C_{24}H_{23}NO$ (341.45): C 84.42, H 6.79, N 4.10; found: C 84.52, H 6.78, N 4.11.

5-Hydroxy-4-(4-methoxyphenyl)-9-'exo'*-(naphthalen-1-yl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decan-3-one* (= rel-*(3aR,4S,6S,7R,7aS)-Octahydro-3-hydroxy-2-(4-methoxyphenyl)-6-(naphthalen-1-yl)-4,7-epoxy-1*H*-indol-1-one*; **14a**). CC (AcOEt/hexane 3:2): **14a** (38%). Colorless crystals. M.p. 199°. IR: 3391, 3011, 2995, 2956, 2833, 1674, 1655, 1611, 1516, 1445, 1416, 1337, 1255, 1181, 1079, 828, 802, 778. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.62–1.68 (*m*, $H_{exo'}$–C(8)); 2.38 (*dd*, *J* = 9.19, 2.73, $H_{endo'}$–C(8)); 3.34 (*d*, H–C(2), H–C(6) with DMSO); 3.75 (*s*, MeO); 3.94 (*dd*, *J* = 4.88, 3.91, $H_{endo'}$–C(9)); 4.69 (*s*, H–C(1)); 4.88 (*d*, *J* = 4.86, H–C(7)); 5.33 (*d*, *J* = 8.41, H–C(5)); 6.45 (*d*, *J* = 8.60, OH); 6.94 (*d*, *J* = 8.90, 2 arom. H); 7.42 (*d*, *J* = 8.90, 2 arom. H); 7.45–7.59 (*m*, 4 arom. H); 7.76 (*d*, *J* = 8.80, 1 arom. H); 7.92 (*d*, *J* = 9.19, 1 arom. H); 8.20 (*d*, *J* = 8.21, 1 arom. H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 39.5; 41.0; 49.5; 51.8; 55.2; 80.5; 83.2; 87.6; 113.7; 123.0; 123.5; 125.0; 125.6; 126.0; 126.4; 128.6; 130.5; 131.0; 133.4; 140.9; 156.9; 172.2. MS: 400 ($M^{+\bullet}$), 205, 190, 189, 154, 67. Anal. calc. for $C_{25}H_{23}NO_4$ (401.45): C 74.79, H 5.77, N 3.49; found: C 74.78, H 5.78, N 3.53.

5-Hydroxy-4-(4-methoxyphenyl)-8-'exo'*-(naphthalen-1-yl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decan-3-one* (= rel-*(3aR,4S,5R,7R,7aS)-Octahydro-3-hydroxy-2-(4-methoxyphenyl)-5-(naphthalen-1-yl)-4,7-epoxy-1*H*-indol-1-one*; **14b**). CC (AcOEt/hexane 3:2): **14b** (50%). Colorless crystals. M.p. 207°. IR: 3245, 3011, 2991, 2973, 2937, 2845, 1655, 1595, 1510, 1458, 1446, 1394, 1252, 1179, 1074, 806, 765, 737. ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.67–1.72 (*m*, $H_{exo'}$–C(9)); 2.43 (*dd*, *J* = 9.19, 2.73, $H_{endo'}$–C(9)); 2.67 (*d*, *J* = 7.82, H–C(6)); 3.14 (*d*, *J* = 7.62, H–C(2)); 3.75 (*s*, MeO); 3.87 (*dd*, *J* = 9.19, 2.73, $H_{endo'}$–C(8)); 4.76 (*d*, *J* = 4.86, H–C(1)); 4.89 (*s*, H–C(7)); 5.35 (*d*, *J* = 8.41, H–C(5)); 6.44 (*d*, *J* = 8.60, OH); 6.95 (*d*, *J* = 8.80, 2 arom. H); 7.42 (*d*, *J* = 8.80, 2 arom. H); 7.45–7.60 (*m*, 4 arom. H); 7.78 (*d*, *J* = 7.62, 1 arom. H); 7.93 (*d*, *J* = 7.62, 1 arom. H); 8.20 (*d*, *J* = 8.21, 1 arom. H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 39.4; 41.6; 50.1; 52.4; 55.7; 79.2; 85.3; 88.0; 114.2; 124.1; 125.5; 126.5; 126.8; 129.1; 131.0; 131.5; 133.9; 141.4; 157.3; 172.8. MS: 400 ($M^{+\bullet}$), 206, 190, 189, 154, 67. Anal. calc. for $C_{25}H_{23}NO_4$ (401.45): C 74.79, H 5.77, N 3.49; found: C 74.78, H 5.77, N 3.51.

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