Additions of Lithiated Alkoxyallenes to Phthalimide: A New Synthesis of Pyrroloisoindolones and an Unusual Olefination Reaction

Silvia Kaden, Hans-Ulrich Reissig,* Irene Brüdgam, Hans Hartl

Freie Universität Berlin, Institut für Chemie und Biochemie, Takustraße 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de

Received 6 October 2005; revised 23 November 2005

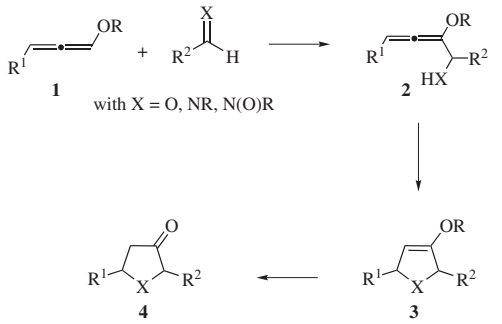
Abstract: Addition of an excess of lithiated alkoxyallenes to phthalimide **5** provided the expected primary adducts **7a–c**, which could be cyclized via their oxygen moiety to furnish spirofuran derivatives **8a–c**. After selective protection of the hydroxyl function of **7a–c** the resulting siloxy derivatives **11a–c** were transformed by gold(III) catalysis into pyrroloisoindolones **13a–c** in moderate yields. This establishes a new approach to this class of heterocycles in a [3+2] fashion with the alkoxyallenes as functionalized C-3 unit and phthalimide **5** providing the CN moiety. Treatment of primary adducts **7a–c** with aqueous sulfuric acid surprisingly led to compounds **14a–c** in good yields. The constitution of these products was proved by an X-ray analysis of derivative **15a**. Aqueous hydrochloric acid converted **7a** into a similar product **17** containing a chlorine substituent. These reactions can be considered as olefination reactions of phthalimide.

Key words: allenes, lithium, imide, pyrroloisoindolones, gold catalysis

Lithiation of alkoxyallenes **1** with *n*-butyllithium and subsequent reactions with electrophiles such as carbonyl compounds, imines or nitrones lead to primary adducts of general structure **2**. Their cyclization (under varying conditions) afford five- or six-membered heterocycles **3** such as furans,[1] pyrroles,[2] and 1,2-oxazine derivatives,[3] which are versatile building blocks due to the reactive enol ether moiety incorporated.[4] The simplest subsequent transformation of **3** is the hydrolysis to heterocyclic ketones **4**, but reactions with other electrophiles or reductions also afford useful products. Overall, alkoxyallenes **1** serve as C-3 unit for the preparation of heterocycles **3** and **4** (Scheme 1).[5] This general approach has been exploited by our group for the synthesis of several natural products[6] or novel carbohydrate mimetics.[7]

Due to the importance of nitrogen containing heterocycles as drugs, new synthetic methods for their construction are a permanent challenge. In this report, we demonstrate that addition of lithiated alkoxyallenes to phthalimide **5** and subsequent reactions provide several interesting classes of tricyclic compounds with pyrroloisoindoles being the most interesting products.

Honma recently reported that substituted pyrroloisoindoles are potent Cdk4 inhibitors.[8] The most common approach to pyrroloisoindolones involves an intramolecular



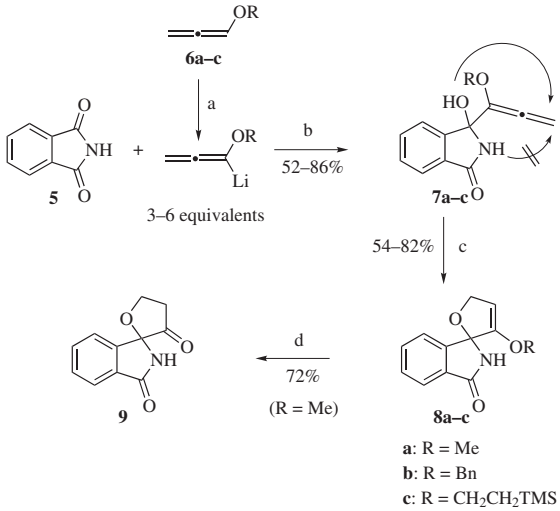
Scheme 1 Syntheses of heterocycles with alkoxyallenes as precursors.

Heck reaction of ortho-halogen-substituted 1-(benzoyl)-1*H*-pyrroles.[8,9] Alternatively, an arylation of *N*-acylpyrroles with equimolar amounts of $Pd(OAc)_2$ in acetic acid also leads to this heterocycles, albeit the desired product is only obtained as minor component.[10] A photoinduced cyclization of *N*-(2-alkenyl)phthalimides and subsequent elimination under acidic conditions also affords these interesting compounds.[10]

Preparation of the Primary Allene Adducts and of Furan Derivatives

It is known that phthalimide **5** smoothly reacts with alkyl- and aryllithium reagents to provide substituted 1-isoindolinones.[11] We therefore examined the additions of the lithiated species derived from alkoxyallene **6a–c** with electrophile **5** (Scheme 2). Employing an excess of the lithiated allenes the primary allene adducts **7a–c** were obtained in moderate to very good yields. Since these intermediates bear two nucleophilic centers, their ring-closing reaction with the allene terminus may lead to either furan or pyrrole derivatives. The standard procedures such as Lewis acid or palladium(II)-catalyzed reactions were examined. Treatment with $AgNO_3$[12] or $Pd(OAc)_2$ in MeCN gave only low yields of spiro compounds **8** or complete decomposition of the starting material. The strongly basic conditions with *t*-BuOK in DMSO[1] provided the new spiro compounds **8a–c** in moderate to good yields. Acidic hydrolysis of the dihydrofuran derivative **8a** furnished dihydrofuran-3-one **9**, which contains a carbonyl group capable of further modifications such as Grignard additions or aldol reactions. Thus, novel heterocyclic spiro com-

SYNTHESIS 2006, No. 8, pp 1351–1359
Advanced online publication: 27.03.2006
DOI: 10.1055/s-2006-926399; Art ID: T14105SS

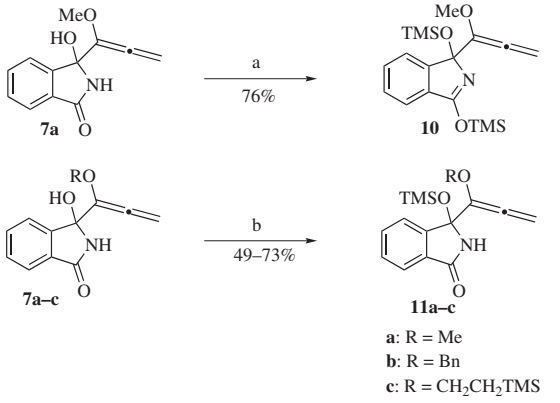


Scheme 2 *Reagents and conditions*: a) *n*-BuLi, THF, –78 °C, 10 min; b) THF, –78 °C to –20 °C, 5 h; c) *t*-BuOK, DMSO, 50 °C, 16 h; d) HCl (6 N), THF, r.t., 2 h, (**8a** → **9**).

pounds may be prepared according to Scheme 2 via intermediates **8** and **9**.

Cyclization to Pyrroloisoindolones

In order to find a method for selective ring-closure reactions involving the nitrogen atom of **7** a selective protection of its tertiary OH function was required. First attempts with **7a** employing TMSOTf as silylating agent only led to low yields for the desired monoprotected product **11a** (Scheme 3). We rather obtained the disilylated compound **10**. The second protection of the amide was proved by ^{29}Si NMR spectroscopy. Optimized reaction conditions with 1.1 equivalents of TMSCl, 1.2 equivalents of Et_3N and 0.25 equivalent of DMAP furnished the desired monoprotected intermediates **11a–c** in 49–73% yield.

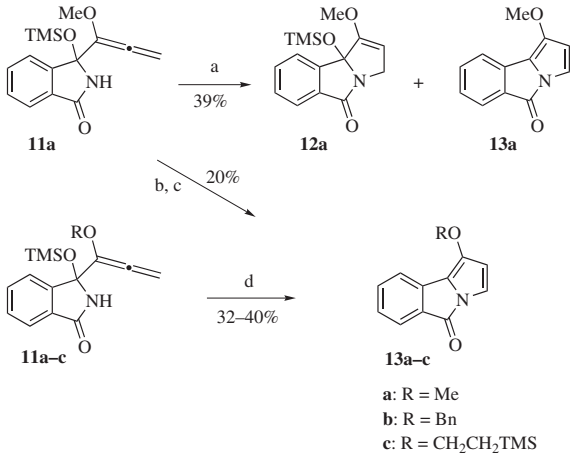


Scheme 3 *Reagents and conditions*: a) TMSOTf, Et_3N, DMAP, CH_2Cl_2, r.t., 2 d; b) TMSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 4 d.

With **11a–c** in hand we were able to examine cyclizations under various conditions. Basic reaction conditions (*t*-BuOK in DMSO at 50 °C) provided only starting material **11a** even after heating for 16 hours. Similarly unsuccessful was Lewis acid catalysis with $AgNO_3$ in MeCN (under light exclusion) or with $Pd(OAc)_2$ in MeCN. A possible explanation for these failures may be the low nucleophilicity of the amide nitrogen compared to amines. Electron-donating or neutral groups at the nitrogen of similar allene adducts facilitated the cyclization.[13]

Silver nitrate in acetone is a considerably stronger promoter which – under light exclusion – gave a mixture of the desired cyclization product **12a**, pyrrole derivative **13a**, and starting material **11a** (Scheme 4). A reaction time longer than nine hours, or the use of more active silver salts such as AgOTf, led to decomposition before completion of the transformation. This may be the reason why yields for product **12a** and pyrrole **13a** were low. Complete conversion of a mixture of **12a** and **13a** into pyrrole derivative **13a** was achieved in 65% yield by treatment of the mixture with $BF_3{\cdot}OEt_2$ (20% overall yield with respect to **11a**).

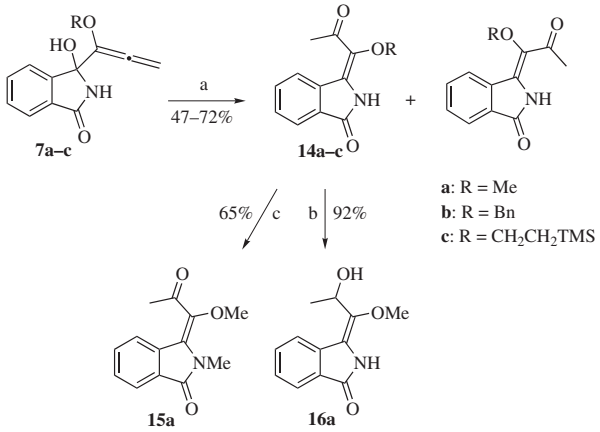
Hashmi reported novel cyclizations of allene derivatives under mild conditions employing gold(III) salts.[14] When we used $AuCl_3$ in a protocol analogous to that of Krause et al.[15] formation of **12a–c** was not observed, instead, pyrroloisoindolones **13a–c** were directly obtained in 32–40% yield. The gold(III) catalyst hence induced cyclization and subsequent (formal) elimination of trimethylsilanol. The moderate stability of these electron-rich pyrrole derivatives could be a reason for the low yields in these reactions. Alternatively, the Lewis acid $AuCl_3$ may also lead to some decomposition of the starting material before its transformation into cyclized product. Despite the moderate yields, the route via **6**, **7**, and **11** (Schemes 2 and 4) allows a straightforward entry to the heterocycles **13**.



Scheme 4 *Reagents and conditions*: a) $AgNO_3$ (0.4 equiv), acetone, 9 h, 4% **13a**, 35% **12a**; b) $AgNO_3$ (0.4 equiv), acetone, 9 h, 31% (**12a** + **13a**); c) $BF_3{\cdot}OEt_2$, Et_2O, 0 °C to r.t., 65%; d) $AuCl_3$ (0.05 equiv) CH_2Cl_2, 0 °C to r.t., 30 min.

Acid-Induced Transformations of Primary Allene Adducts

When primary allene adducts **7a–c** were treated with aqueous sulfuric acid, a rather unexpected product class was obtained (Scheme 5). Methyl ketones **14a–c** were isolated as *E*/*Z* mixtures ranging from 88:12 to 99:1 depending on the alkoxy substituents involved. Elucidation of the proposed constitution by analytical data proved to be rather difficult. Treatment of **14a** with $CeCl_3$ and $NaBH_4$ in methanol furnished the secondary alcohol **16a**, which proved the methyl ketone moiety of the precursor, but not the overall structure. Finally, we could gain suitable crystals by N-methylation of **14a** which furnished compound **15a** in good yield. Its X-ray analysis (Figure 1) unambiguously proved the constitution and configuration and thus also the structure of precursor **14a**. Overall, the addition of lithiated alkoxyallenes and the subsequent acid treatment constitute a rather unusual olefination of one of the two phthalimide carbonyl groups.



Scheme 5 *Reagents and conditions*: a) 2 N H_2SO_4, THF, r.t., 2 d; b) $CeCl_3$, $NaBH_4$, MeOH, 0 °C to r.t., 4 h; c) Me_2SO_4, K_2CO_3, acetone, 12 h, r.t., 24 h, reflux.

As mechanism of the transformation **7** → **14** we suggest a protonation of the hydroxyl group of **14** and subsequent displacement of water forming a sufficiently stabilized carbenium ion (Scheme 6). The two mesomeric formulas depicted demonstrate that the central carbon of the allene moiety is now capable to accept a nucleophile. Addition of water leads to an enol which subsequently tautomerizes to furnish **14**. This kind of umpolung of alkoxyallene units (by converting the central carbon from a nucleophilic unit into a electrophilic centre) has also been observed in the reaction of lithiated alkoxyallenes with nitriles followed by trifluoroacetic acid treatment, which unexpectedly leads to formation of highly substituted pyridine derivatives.[16]

By switching from sulfuric acid to hydrochloric acid, the chloride ions present are sufficiently nucleophilic to be incorporated into the products. Primary allene adduct **7a** was smoothly converted into an *E*/*Z* mixture of **17** (Scheme 7).

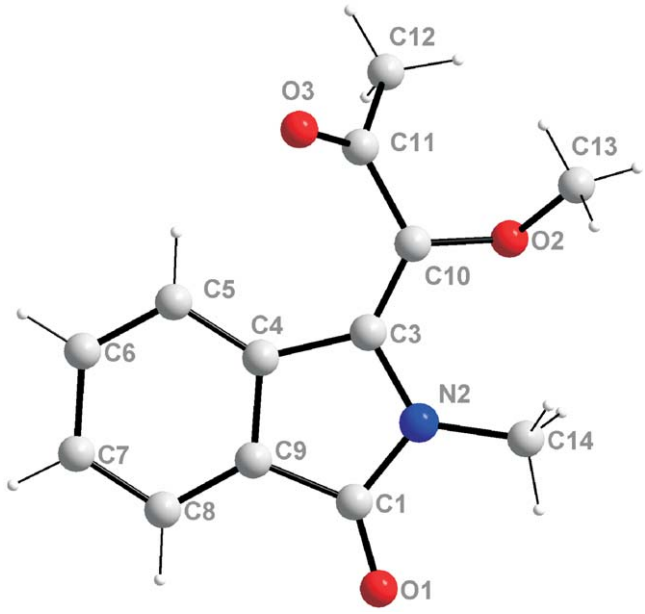
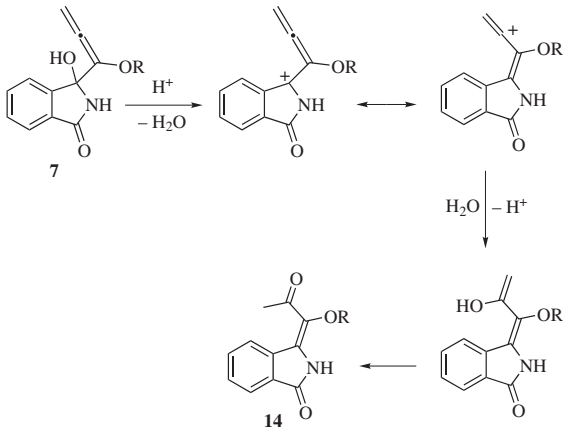
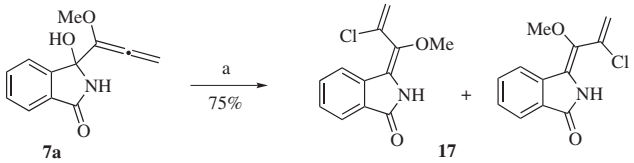


Figure 1 Crystal structure of the N-methylated compound **15a**



Scheme 6 Proposed mechanism for the treatment of the primary allene adducts **7** with acid leading to compounds **14**.



Scheme 7 *Reagents and conditions*: a) 2 N HCl, CH_2Cl_2, r.t., 2 d, *Z*/*E* = 81:19.

In summary we have found a new route to the class of pyrroloisoindolones **13** using the addition of the lithiated species derived from alkoxyallenes **6** to phthalimide **5** as electrophile. We could also prepare the interesting tricyclic spirofuran derivatives **8** and **9**. Surprisingly, primary allene adducts **7** could be converted into alkenes **14** by an unusual acid-catalyzed transformation which overall constitutes an olefination of **5**. These reactions demonstrate again the synthetic versatility of lithiated alkoxyallenes as

C-3 building blocks leading to expected and unexpected products.[5]

Unless otherwise stated all reactions were performed under argon in flame-dried flasks by adding the components via syringes. All solvents were dried using standard procedures. IR spectra were measured with a Perkin-Elmer FT-IR spectrometer Nicolet 5 SXC with DTGS-detector. ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments (WH 270, AC 250, AC 500) and Jeol Eclipse 500. Proton chemical shifts are reported in ppm relative to TMS (δ = 0.00) or to $CHCl_3$ (δ = 7.26). Higher order NMR spectra are approximately interpreted as first-order spectra if possible. ^{13}C chemical shifts are reported relative to $CDCl_3$ (δ = 77.0). ^{29}Si NMR spectra were recorded on a Bruker instrument (AC 500) in CD_3OD. MS and HRMS analyses were performed on Finnigan MAT 711 (EI, 8 kV) and MAT CH7A (EI, 3 kV) spectrometers at 80 eV. UV spectra were measured with a Varian Cary 50 in CH_2Cl_2. Neutral Al_2O_3 (activity III, Fluka or Merck) or silica gel (0.040–0.063 mm, Fluka) were used for column chromatography. Nucleosil 50-5 (Macherey & Nagel) was used for HPLC. Melting points were measured with a Reichert Thermopan and are uncorrected. Starting materials methoxyallene (**6a**),[17] benzyloxyallene (**6b**)[3] and TMSE-allene (**6c**)[3] were prepared by literature procedures. All other chemicals were commercially available and were used as received.

3-Hydroxy-3-(1-methoxypropa-1,2-dienyl)isoindolin-1-one (7a)

n-BuLi (2.3 M, 4.39 mL, 10.1 mmol) was added to a solution of methoxyallene (**6a**; 710 mg, 10.1 mmol) in THF (10 mL) at –78 °C. The solution was stirred for 10 min before adding isoindole-1,3-dione (**5**; 500 mg, 3.39 mmol) and the mixture was stirred for 5 h at –60 °C. After addition of sat. aq $NaHCO_3$ solution (20 mL), the layers were separated and the aqueous layer was extracted with EtOAc–MeOH (5:1, 3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product was recrystallized from MeOH to give 600 mg (82%) of **7a** as yellow solid; mp 165–170 °C.

IR (KBr): 3270 (OH, CONH), 3010–2830 (CH), 1950 (C=C=C), 1690 (C=O) cm^{-1}.

^{1}H NMR (CD_3OD, 250 MHz): δ = 3.42 (s, 3 H, OCH_3), 4.88 (br s, 2 H, NH, OH), 5.63 (d, *J* = 9.1 Hz, 1 H, 3′-H), 5.66 (d, *J* = 9.1 Hz, 1 H, 3′-H), 7.46–7.72 (m, 4 H, Ar).

^{13}C NMR (CD_3OD, 62.9 MHz): δ = 57.1 (q, OCH_3), 86.9 (s, C-3), 94.4 (t, C-3′), 132.1 (s, C-3a), 123.8, 124.4, 130.6, 133.6 (4 d, C-4, C-5, C-6, C-7), 135.6 (s, C-1′), 149.3 (s, C-7a), 171.6 (s, C=O), 198.0 (s, C-2′).

MS (EI, 80 eV, 135 °C): *m*/*z* (%) = 217 (10, [M$^+$]), 216 (18, [M$^+$ – H]), 188 (39), 148 (61, [M$^+$ – C_4H_5O]), 130 (100, [M$^+$ – $C_4H_7O_2$]), 102 (26), 55 (15).

Anal. Calcd for $C_{12}H_{11}NO_3$ (217.2): C, 66.35; H, 5.10; N, 6.44. Found: C, 66.06; H, 4.96; N, 6.24.

3-[1-(Benzyloxy)propa-1,2-dienyl]-3-hydroxyisoindolin-1-one (7b)

n-BuLi (2.5 M, 4.74 mL, 11.9 mmol) was added to a solution of benzyloxyallene (**6b**; 1.98 g, 13.6 mmol) in THF (35 mL) at –78 °C. The solution was stirred for 15 min before adding isoindole-1,3-dione (**5**; 500 mg, 3.39 mmol). The mixture was stirred for 4 h and allowed to warm up from –78 to –20 °C. After addition of H_2O (30 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to yield 850 mg (86%) of **7b** as pale yellow solid; mp 135–140 °C.

IR (KBr): 3210 (OH, CONH), 3080–2860 (CH), 1955 (C=C=C), 1675 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.62 (s, 2 H, CH_2Ph), 4.70 (br s, 1 H, NH), 5.53 (s, 2 H, 3′-H), 7.16–7.29 (m, 5 H, C_6H_5), 7.36–7.65 (m, 4 H, Ar); the signal for OH was not detected.

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 71.2 (t, *C*H_2Ph), 85.5 (s, C-3), 94.5 (t, C-3′), 123.2, 123.3, 127.5, 127.7, 128.2, 129.5 (6 d, Ar), 130.4 (s, C-1′), 132.4 (s, C-3a), 136.6 (s, C_6H_5), 146.5 (s, C-7a), 169.3 (s, C=O), 196.0 (s, C-2′).

MS (EI, 80 eV, 140 °C): *m*/*z* (%) = 293 (1, [M$^+$]), 275 (1, [M$^+$ – H_2O]), 247 (2), 202 (2, [M$^+$ – C_7H_7]), 148 (31, [$C_8H_6NO_2^+$]), 130 (30), 91 (100, [$C_7H_7^+$]).

HRMS (EI, 80 eV, 140 °C): *m*/*z* calcd for $C_{18}H_{15}NO_3$ [M$^+$]: 293.1051; found: 293.1062.

3-[1-(2-Trimethylsilylethoxy)propa-1,2-dienyl]-3-hydroxyisoindolin-1-one (7c)

n-BuLi (2.5 M, 0.91 mL, 2.29 mmol) was added to a solution of TMSE-allene (**6c**; 423 mg, 2.71 mmol) in THF (15 mL) at –78 °C. The solution was stirred for 15 min before adding isoindole-1,3-dione (**5**; 200 mg, 1.35 mmol). The mixture was stirred for 4 h and allowed to warm up from –78 to –20 °C. After addition of H_2O (20 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to yield 211 mg (52%) of **7c** as pale yellow solid; mp 118–120 °C.

IR (KBr): 3250–3100 (OH, CONH), 3000–2850 (CH), 1955 (C=C=C), 1685 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = –0.03 [s, 9 H, $Si(CH_3)_3$], 1.00 (m_c, 2 H, CH_2TMS), 1.67 (br s, 1 H, OH), 3.64–3.76 (m, 2 H, OCH_2), 5.54 (s, 2 H, 3′-H), 6.52 (br s, 1 H, NH), 7.42–7.74 (m, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = –1.44 [q, $Si(CH_3)_3$], 17.7 (t, *C*H_2TMS), 67.6 (t, OCH_2), 85.4 (s, C-3), 94.1 (t, C-3′), 123.3, 123.5, 129.8, 132.6 (4 d, C-4, C-5, C-6, C-7), 130.5 (s, C-1′), 132.5 (s, C-3a), 146.6 (s, C-7a), 169.0 (s, C=O), 195.8 (s, C-2′).

MS (EI, 80 eV, 140 °C): *m*/*z* (%) = 303 (1, [M$^+$]), 275 (5, [M$^+$ – C_2H_4]), 260 (8, [M$^+$ – CONH]), 221 (22), 148 (12, [$C_8H_5NO_2^+$]), 130 (20), 73 (100, [TMS$^+$]), 45 (15, [$C_2H_5O^+$]).

HRMS (EI, 80 eV, 140 °C): *m*/*z* calcd for $C_{15}H_{21}NO_2Si$ [M$^+$ – CO]: 275.1341; found: 275.1357.

Cyclization Reactions of Allenes 7a–c; General Procedure

The allene adduct (1 equiv) was dissolved in DMSO and freshly sublimed *t*-BuOK (0.27 equiv) was added. The dark brown mixture was stirred for 16 h at 50 °C. The solution was quenched with sat. aq $NaHCO_3$ solution (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvents were removed in vacuo.

4′-Methoxy-3a,7a-benzo-1′-oxa-2-azaspiro[4,4]non-3′-en-1-one (8a)

According to the general procedure, treatment of allene adduct **7a** (200 mg, 0.92 mmol) in DMSO (6 mL) with *t*-BuOK (29 mg, 0.25 mmol) and purification by recrystallization (MeOH–hexane, 1:1) gave 165 mg (82%) of **8a** as yellow solid; mp 214 °C.

IR (KBr): 3200 (CONH), 3100–2840 (CH, =C–H), 1710 (C=O), 1700 (C=C) cm^{-1}.

^{1}H NMR (CD_3OD, 250 MHz): δ = 3.64 (s, 3 H, OCH_3), 4.77 (d, *J* = 1.6 Hz, 2 H, 2′-H), 5.27 (t, *J* = 1.6 Hz, 1 H, 3′-H), 7.41 (d, *J* = 7.5 Hz, 1 H, Ar), 7.51–7.55 (m, 1 H, Ar), 7.59–7.63 (m, 1 H,

Ar), 7.69 (d, *J* = 7.5 Hz, 1 H, Ar); the signal for NH was not detected.

^{13}C NMR (CD_3OD, 62.9 MHz): δ = 58.5 (q, OCH_3), 72.5 (t, C-2′), 95.9 (d, C-3′), 98.1 (s, C-3), 123.7, 123.8, 131.0, 133.9 (4 d, C-4, C-5, C-6, C-7), 132.7 (s, C-3a), 147.5 (s, C-7a), 154.6 (s, C-4′), 171.6 (s, C=O).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 217 (27, [M$^+$]), 202 (22, [M$^+$ – Me]), 188 (20), 130 (13, [M$^+$ – $C_4H_7O_2$]), 103 (14), 87 (17), 76 (19, [M$^+$ – $C_6H_7NO_3$]), 55 (100, [M$^+$ – $C_{10}H_{10}O_2$]), 27 (13, [M$^+$ – $C_{11}H_{10}O_3$]).

HRMS (EI, 80 eV, 100 °C): *m*/*z* calcd for $C_{12}H_{11}NO_3$ [M$^+$]: 217.0739; found: 217.0753.

4′-Benzyloxy-3a,7a-benzo-1′-oxa-2-azaspiro[4,4]non-3′-en-1-one (8b)

According to the general procedure, treatment of allene adduct **7b** (100 mg, 0.34 mmol) in DMSO (5 mL) with *t*-BuOK (10 mg, 0.09 mmol) and purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 98:2) afforded 77 mg (77%) of **8b** as yellow oil.

IR (film): 3260 (CONH), 3090–2870 (CH, =C–H), 1710 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.73 (s, 2 H, C*H*$_2$Ph), 4.84 (m$_c$, 2 H, 2′-H), 5.07 (m$_c$, 1 H, 3′-H), 6.92 (s, 1 H, NH), 7.07–7.26 (m, 5 H, C_6H_5), 7.30–7.81 (m, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 71.2, 72.2 (2 t, *C*H$_2$Ph, C-2′), 95.9 (d, C-3′), 96.5 (s, C-3), 122.3, 127.9, 131.8, 135.5 (4 d, C-4, C-5, C-6, C-7), 123.2, 126.8, 128.3, 131.1 (3 d, s, C_6H_5), 135.5, 145.6 (2 s, C-3a, C-7a), 151.6 (s, C-4′), 169.3 (s, C=O).

MS (EI, 80 eV, 110 °C): *m*/*z* (%) = 293 (5, [M$^+$]), 275 (2, [M$^+$ – H_2O]), 237 (7, [M$^+$ – C_3H_3O]), 147 (24, [M$^+$ – $C_8H_5NO_2$]), 104 (27, [$C_7H_4O^+$]), 91 (100, [$C_7H_7^+$]), 76 (42, [$C_6H_4^+$]), 54 (30), 50 (32).

HRMS (EI, 80 eV, 110 °C): *m*/*z* calcd for $C_{18}H_{15}NO_3$ [M$^+$]: 293.1051; found: 293.1049.

4′-(2-Trimethylsilyl)ethoxy-3a,7a-benzo-1′-oxa-2-azaspiro[4,4]non-3′-en-1-one (8c)

According to the general procedure, treatment of allene adduct **7c** (60 mg, 0.20 mmol) in DMSO (5 mL) with *t*-BuOK (6 mg, 0.05 mmol) yielded after purification by column chromatography (CH_2Cl_2–MeOH, 98:2) 33 mg (54%) of **8c** as yellow oil.

IR (film): 3250 (CONH), 2950–2870 (CH, =C–H), 1710 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = –0.18 [s, 9 H, $Si(CH_3)_3$], 0.74–0.97 (m, 2 H, C*H*$_2$TMS), 3.75–3.95 (m, 2 H, OCH_2), 4.77 (dd, *J* = 11.3, 1.6 Hz, 1 H, 2′-H), 4.79 (dd, *J* = 11.3, 1.7 Hz, 1 H, 2′-H), 5.00 (m$_c$, 1 H, 3′-H), 6.61 (s, 1 H, NH), 7.31–7.37 (m, 1 H, Ar), 7.40–7.56 (m, 2 H, Ar), 7.71–7.77 (m, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = –1.6 [q, $Si(CH_3)_3$], 16.9 (t, *C*H$_2$TMS), 68.6, 71.4 (2 t, OCH_2, C-2′), 94.0 (d, C-3′), 96.5 (C-3), 122.4, 123.3, 129.7, 131.2, 132.5 (4 d, s, C-4, C-5, C-6, C-7, C-3a), 145.8 (s, C-7a), 152.3 (s, C-4′), 169.1 (s, C=O).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 303 (1, [M$^+$]), 288 (1, [M$^+$ – Me]), 275 (4, [M$^+$ – CO]), 260 (8, [M$^+$ – CONH]), 221 (64, [M$^+$ – $C_{11}H_{11}NO_4$]), 73 (100, [TMS$^+$]), 55 (12), 45 (11).

Anal. Calcd for $C_{16}H_{21}NO_3Si$ (303.3): C, 63.33; H, 6.58; N, 4.62. Found: C, 63.29; H, 6.98; N, 4.43.

3a,7a-Benzo-1′-oxa-2-azaspiro[4,4]non-3′-ene-1,4′-dione (9)

Compound **8a** (400 mg, 1.84 mmol) was dissolved in THF (15 mL) and 6 N HCl (10.4 mL) was added. The solution was stirred at r.t. for 2 h and then quenched with sat. aq Na_2CO_3 solution (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product **9** was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to yield 272 mg (72%) of **9** as yellow oil.

IR (film): 3500–2990 (CONH, CH), 2970–2845 (CH_3, OCH_2CH_2), 1760, 1700 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.74 (t, *J* = 6.8 Hz, 2 H, 3′-H), 4.26–4.49 (m, 2 H, 2′-H), 7.20–7.27 (m, 1 H, Ar), 7.36–7.51 (m, 2 H, Ar), 7.65–7.72 (m, 1 H, Ar), 8.39 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 35.4 (t, C-3′), 63.8 (t, C-2′), 90.6 (s, C-3), 122.6, 123.7, 130.4, 132.8 (4 d, C-4, C-5, C-6, C-7), 131.7 (s, C-3a), 143.5 (s, C-7a), 170.5 (s, C-1), 208.6 (s, C-4′).

MS (+ FAB): *m*/*z* (%) = 226 (21, [M$^+$ + Na]), 204 (100, [M$^+$ + H]), 148 (23, $C_8H_5NO_2^+$).

Anal. Calcd for $C_{11}H_9NO_3$ (203.1): C, 65.02; H, 4.46; N, 6.89. Found: C, 64.14; H, 4.40; N, 6.65 (No better elemental analysis could be obtained).

1-(1-Methoxypropa-1,2-dienyl)-1,3-bis(trimethylsilyloxy)-1*H*-isoindole (10)

The allene adduct **7a** (500 mg, 2.30 mmol) was dissolved in CH_2Cl_2 (25 mL) and Et_3N (0.63 mL, 4.60 mmol) and DMAP (70 mg, 0.57 mmol) were added. The solution was cooled to 0 °C and TMSOTf (0.80 mL, 4.20 mmol) was added. The mixture was stirred for 2 d at r.t. After addition of H_2O, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and Et_2O (20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvents were removed in vacuo. The crude product was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 98:2) and gave 607 mg (76%) of **10** as colorless oil, which crystallized in the refrigerator; mp 153–155 °C .

IR (film): 3215–3000 (CH), 1960 (C=C=C), 1720 (C=N) cm^{-1}.

^{1}H NMR (CD_3OD, 250 MHz): δ = –0.03 [s, 9 H, $Si(CH_3)_3$], 0.13 [s, 9 H, $Si(CH_3)_3$], 3.41 (s, 3 H, OCH_3), 4.87 (s, 1 H, NH), 5.66 (d, *J* = 8.2 Hz, 1 H, 3′-H), 5.73 (d, *J* = 8.2 Hz, 1 H, 3′-H), 7.52–7.74 (m, 4 H, Ar).

^{13}C NMR (CD_3OD, 62.9 MHz): δ = –1.1, 1.2 [2 q, $Si(CH_3)_3$], 56.0 (q, OCH_3), 94.0 (t, C-3′), 132.2 (s, C-3a), 123.9, 124.8, 130.7, 133.6 (4 d, C-4, C-5, C-6, C-7), 136.3 (s, C-1′), 149.5 (s, C-7a), 171.7 (s, C-1), 198.4 (s, C-2′); the signal for C-3 was not unambiguously detected.

^{29}Si NMR (CD_3OD, 99 MHz): δ = 18.74 [s, $OSi(CH_3)_3$], 22.64 [s, $OSi(CH_3)_3$].

MS (EI, 80 eV, 135 °C): *m*/*z* (%) = 361 (4, [M$^+$]), 345 (4, [M$^+$ – CH_3]), 292 (22, [M$^+$ – C_4H_5O]), 274 (16), 260 (44, [M$^+$ – $(CH_3)_3SiOC$]), 244 (24), 220 (100, [M$^+$ + H – C_4H_5O – TMS]), 204 (20, [M$^+$ + H – C_4H_5O – OTMS]), 130 (24), 73 (71, [TMS$^+$]), 31 (10, [MeO$^+$]).

HRMS (EI, 80 eV, 135 °C): *m*/*z* calcd for $C_{18}H_{27}NO_3Si_2$ [M$^+$]: 361.1529; found: 361.1542.

Mono-TMS Protection of 7a–c; General Procedure

The primary allene adduct **7** (1 equiv) was dissolved in CH_2Cl_2 (15 mL/mmol) and Et_3N (1.2 equiv) and DMAP (0.25 equiv) were added at r.t. The solution was cooled to 0 °C and TMSCl (1.1 equiv) was added. The mixture was stirred for 4 d at r.t. After addition of H_2O, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 and Et_2O. The combined organic extracts were dried ($MgSO_4$) and the solvents were removed in vacuo.

3-(1-Methoxypropa-1,2-dienyl)-3-(trimethylsilyloxy)-2,3-dihydroisoindol-1-one (11a)

According to the general procedure, treatment of allene adduct **7a** (200 mg, 0.92 mmol) with Et_3N (178 μL, 1.28 mmol), DMAP (28 mg, 0.23 mmol) and a solution of TMSCl (120 μL, 1.01 mmol) in CH_2Cl_2 (14 mL) yielded crude **11a**. After purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 98:2) 194 mg (73%) of **11a** was obtained as pale yellow solid (melting range 142–150 °C).

IR (KBr): 3390 (CONH), 3200–2850 (CH), 1960 (C=C=C), 1725 (C=O) cm^{-1}.

^1H NMR (CD_3OD, 250 MHz): δ = –0.06 [s, 9 H, $Si(CH_3)_3$], 3.39 (s, 3 H, OCH_3), 4.85 (s, 1 H, NH), 5.49 (d, *J* = 9.5 Hz, 1 H, 3′-H), 5.52 (d, *J* = 9.5 Hz, 1 H, 3′-H), 7.46–7.73 (m, 4 H, Ar).

^{13}C NMR (CD_3OD, 62.9 MHz): δ = 1.2 [q, $Si(CH_3)_3$], 57.1 (q, OCH_3), 88.4 (s, C-3), 94.0 (t, C-3′), 123.9, 124.8, 130.7, 133.7 (4 d, C-4, C-5, C-6, C-7), 132.5 (s, C-3a), 136.3 (t, C-1′), 149.6 (s, C-7a), 171.8 (s, C=O), 198.5 (s, C-2′).

MS (EI, 80 eV, 135 °C): *m*/*z* (%) = 289 (11, [M^+]), 274 (17, [M^+ – Me]), 260 (36), 244 (18), 220 (100, [$M^+ – C_4H_5O$]), 216 (10, [M^+ – TMS]), 130 (15), 73 (33, [TMS^+]).

Anal. Calcd for $C_{15}H_{19}NO_3Si$ (289.3): C, 62.25; H, 6.62; N, 4.84. Found: C, 62.15; H, 6.47; N, 4.73.

3-[1-(Benzyloxy)propa-1,2-dienyl]-3-(trimethylsilyloxy)isoindolin-1-one (11b)

According to the general procedure, treatment of allene adduct **7b** (200 mg, 0.682 mmol) with Et_3N (133 μL, 0.955 mmol), DMAP (21 mg, 0.17 mmol) and a solution of TMSCl (89 μL, 0.75 mmol) in CH_2Cl_2 (14 mL) yielded the crude product **11b**. After purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 98:2), 182 mg (73%) of **11b** was obtained as colorless solid; mp 135–137 °C.

IR (KBr): 3380 (CONH), 3200–3000 (CH), 1960 (C=C=C), 1710 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = –0.03 [s, 9 H, $Si(CH_3)_3$], 4.63 (s, 2 H, C*H*$_2$Ph), 5.52 (d, *J* = 8.6 Hz, 1 H, 3′-H), 5.54 (d, *J* = 8.6 Hz, 1 H, 3′-H), 6.44 (br s, 1 H, NH), 7.21–7.33 (m, 5 H, C_6H_5), 7.45–7.78 (m, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 1.2 [q, $Si(CH_3)_3$], 71.0 (t, *C*H_2Ph), 86.5 (s, C-3), 93.8 (t, C-3′), 123.3, 124.1, 127.4*, 127.7, 128.3*, 129.5, 132.3 (7 d, C-4, C-5, C-6, C-7, C_6H_5), 130.4 (s, Ar), 133.6 (s, C-3a), 137.1 (s, C-1′), 147.5 (s, C-7a), 169.2 (s, C=O), 196.8 (s, C-2′); * higher intensity.

MS (EI, 80 eV, 120 °C): *m*/*z* (%) = 365 (1, [M^+]), 350 (2, [M^+ – Me]), 335 (6, [M^+ – 2 Me]), 274 (6, [$M^+ – C_7H_7$]), 220 (78), 91 (58, [$C_7H_7^+$]), 73 (100, [TMS^+]), 45 (12).

Anal. Calcd for $C_{21}H_{23}NO_3Si$ (365.1): C, 69.01; H, 6.34; N, 3.83. Found: C, 69.02; H, 6.35; N, 3.77.

3-{1-[(2-Trimethylsilyl)ethoxy]propa-1,2-dienyl}-3-(trimethylsilyloxy)isoindolin-1-one (11c)

According to the general procedure, treatment of allene adduct **7c** (100 mg, 0.33 mmol) with Et_3N (60 μL, 0.43 mmol), DMAP (10 mg, 0.08 mmol) and a solution of TMSCl (43 μL, 0.36 mmol) in CH_2Cl_2 (7 mL) yielded the crude product **11c**. After purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 98:2) 60 mg (49%) of **11c** was obtained as yellow resin.

IR (film): 3270 (CONH), 3080–2890 (CH), 1940 (C=C=C), 1710 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = –0.06 [s, 9 H, $Si(CH_3)_3$], –0.04 [s, 9 H, $Si(CH_3)_3$], 0.95 (m_c, 2 H, C*H*$_2$TMS), 3.62 (t, *J* = 7.8 Hz, 2 H, OCH_2), 5.44 (d, *J* = 10.9 Hz, 1 H, 3′-H), 5.47 (d, *J* = 10.9 Hz, 1 H, 3′-H), 6.54 (br s, 1 H, NH), 7.40–7.77 (m, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = –1.3 [q, $Si(CH_3)_3$], 1.2 [q, $Si(CH_3)_3$], 17.5 (t, CH_2Si), 67.2 (t, OCH_2), 86.6 (s, C-3), 92.8 (t, C-3′), 123.3, 124.1, 129.4, 132.2 (4 d, C-4, C-5, C-6, C-7), 130.4 (s, C-1′), 133.0 (s, C-3a), 147.6 (s, C-7a), 169.1 (s, C=O), 197.0 (s, C-2′).

MS (+ FAB, 80 eV, 100 °C): *m*/*z* (%) = 398 (1, [M^+ + Na]), 376 (4, [M^+ + H]), 73 (100, [TMS^+]).

Anal. Calcd for $C_{19}H_{29}NO_3Si_2$ (375.2): C, 60.76; H, 7.78; N, 3.73. Found: C, 60.70; H, 6.91; N, 3.41 (No better elemental analysis could be obtained).

Methoxy-9b-trimethylsilyloxy-3,9b-dihydropyrrolo[2,1-*a*]isoindol-5-one (12a)

Compound **11a** (255 mg, 0.88 mmol) was dissolved in anhyd acetone (8 mL) and $AgNO_3$ (60 mg, 0.35 mmol) was added. The mixture was stirred for 9 h at r.t. under exclusion of light. The mixture was filtered through Celite and washed with EtOAc. The solvents were removed in vacuo. Purification of the crude material by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) yielded 6 mg (4%) of pyrrole **13a** as yellow solid and 87 mg (35%) of **12a** as yellow oil.

IR (film): 3360 (=CH), 2955, 2850 (CH), 1775 (CONH), 1720 (C=C, C=O) cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = –0.06 [s, 9 H, $Si(CH_3)_3$], 3.66 (s, 3 H, OCH_3), 4.03, 4.39 (2 d, *J* = 14.5 Hz, each 1 H, 3-H), 4.66 (s, 1 H, 2-H), 7.36–7.81 (m, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 0.7 [q, $Si(CH_3)_3$], 47.3 (t, C-3), 57.4 (q, OCH_3), 94.6 (s, C-9b), 107.4 (s, C-9a), 119.4, 123.5, 132.7, 134.7 (4 d, Ar), 129.4 (d, C-2), 131.7 (s, C-5a), 147.2 (s, C-1), 158.1 (s, C=O).

MS (EI, 80 eV, 60 °C): *m*/*z* (%) = 289 (11, [M^+]), 274 (2, [M^+ – Me]), 258 (4, [M^+ – OMe]), 199 (18, [M^+ – TMSO]), 184 (27), 147 (16), 130 (13, [$C_8H_4NO_2^+$]), 91 (30, [$C_7H_7^+$]), 75 (75, [$C_2H_7OSi^+$]), 73 (41, [TMS^+]), 43 (52, [$COMe^+$]), 28 (100, [CO^+]).

HRMS (EI, 80 eV, 60 °C): *m*/*z* calcd for $C_{15}H_{19}NO_3Si$ [M^+]: 289.1134; found: 289.1142.

Conversion of a Mixture of 12a and 13a into Pyrrole 13a

A mixture of unseparated **12a** and **13a** (30 mg, 3:1 according to NMR) was dissolved in Et_2O (10 mL). The mixture was cooled to 0 °C and $BF_3{\cdot}Et_2O$ (17 μL, 0.15 mmol) was added. After stirring for 1 h and warming up to r.t., H_2O was added (5 μL) and the solvents were removed in vacuo. Purification of the crude material by column chromatography on silica gel (CH_2Cl_2–MeOH, 98:2) yielded 13 mg (65%) of **13a** as orange-yellow oil (for spectroscopic and analytical data, see below).

Cyclization of 11a–c to Pyrroles 13a–c; General Procedure

The protected allene **11** (1 equiv) was dissolved under argon in anhyd CH_2Cl_2 (16 mL/mmol) and cooled to 0 °C. Then $AuCl_3$ (0.05 equiv) was added. The reaction was monitored by TLC. After complete consumption of starting material, the solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 99:1).

1-Methoxy-5*H*-pyrrolo[2,1-*a*]isoindol-5-one (13a)

According to the general procedure, treatment of **11a** (100 mg, 0.345 mmol) with $AuCl_3$ (6 mg, 0.019 mmol) in CH_2Cl_2 (4 mL) yielded 28 mg (40%) of **13a** as orange-yellow oil, which crystallized in the refrigerator; mp 55–57 °C.

IR (KBr): 3280 (=CH), 2940 (CH), 1735 (C=O), 1630 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.90 (s, 3 H, OCH_3), 5.95 (d, *J* = 3.6 Hz, 1 H, 2-H), 6.90 (d, *J* = 3.6 Hz, 1 H, 3-H), 6.99–7.73 (m, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 58.7 (q, OCH_3), 107.6 (d, C-2), 116.4 (d, C-3), 119.6, 125.5, 125.8, 134.2 (4 d, C-6, C-7, C-8, C-9), 130.7 (s, C-5a), 136.0 (s, C-9b), 146.4 (s, C-1), 162.6 (s, C-5); the signal for C-9a was not detected.

MS (EI, 80 eV, 50 °C): *m*/*z* (%) = 199 (80, [M^+]), 183 (100, [M^+ – Me]), 130 (27, [$C_8H_4NO_2^+$]), 102 (25), 76 (10, [$C_6H_4^+$]), 43 (14, [$CHNO^+$]), 28 (28, [CO^+]).

UV (CH_2Cl_2): λ_{max} (ε) = 232 (17675), 257 (17358), 264 (17257), 298 (12257), 417 nm (2441).

HRMS (EI, 80 eV, 50 °C): *m*/*z* calcd for $C_{12}H_9NO_2$ [M^+]: 199.0633; found: 199.0642.

1-(Benzyloxy)-5*H*-pyrrolo[2,1-*a*]isoindol-5-one (13b)

According to the general procedure, treatment of **11b** (92 mg, 0.251 mmol) with $AuCl_3$ (4 mg, 0.013 mmol) in CH_2Cl_2 (4 mL) yielded 27 mg (40%) of **13b** as orange-yellow solid; mp 77–80 °C.

IR (KBr): 3110–3000 (=CH), 2930 (CH), 1725 (C=O), 1590 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.13 (s, 2 H, C*H*$_2$Ph), 5.97 (d, *J* = 3.4 Hz, 1 H, 2-H), 6.90 (d, *J* = 3.4 Hz, 1 H, 3-H), 7.06–7.11 (m, 1 H, Ar), 7.27–7.45 (m, 7 H, Ar, Ph), 7.59–7.63 (m, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 73.2 (t, *C*H_2Ph), 108.4 (d, C-2), 116.3 (d, C-3), 119.7, 125.6, 125.7, 127.4, 128.2, 128.6, 134.3 (7 d, C-6, C-7, C-8, C-9, C_6H_5), 130.7 (s, C-5a), 135.9, 136.6 (2 s, C_6H_5, C-9b), 145.0 (s, C-1), 162.7 (s, C-5); the signal for C-9a was not detected.

MS (EI, 80 eV, 70 °C): *m*/*z* (%) = 275 (50, [M^+]), 184 (44, [M^+ – C_7H_7]), 132 (11), 130 (29, [$C_8H_4NO^+$]), 102 (26, [$C_7H_4N^+$]), 90 (100, [$C_7H_7^+$]).

HRMS (EI, 80 eV, 70 °C): *m*/*z* calcd for $C_{17}H_{11}NO_2$ [M^+]: 275.0946; found: 275.0952.

1-(2-Trimethylsilyl)ethoxy-5*H*-pyrrolo[2,1-*a*]isoindol-5-one (13c)

According to the general procedure, treatment of **11c** (123 mg, 0.327 mmol) with $AuCl_3$ (6 mg, 0.019 mmol) in CH_2Cl_2 (6 mL) yielded 30 mg (32%) of **13c** as orange-yellow oil which solidified in the refrigerator.

IR (film): 3110–2895 (CH), 1740 (C=O), 1620 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.12 [s, 9 H, $Si(CH_3)_3$], 1.14 (t, *J* = 8.0 Hz, 2 H, C*H*$_2$TMS), 4.18 (t, *J* = 8.0 Hz, 2 H, OCH_2), 5.84 (d, *J* = 3.4 Hz, 1 H, 2-H), 6.91 (d, *J* = 3.4 Hz, 1 H, 3-H), 7.07 (m_c, 1 H, Ar), 7.14 (m_c, 1 H, Ar), 7.61 (br d, *J* = 7.5 Hz, 1 H, Ar), 7.66 (d, *J* = 7.5 Hz, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = –1.2 [q, $Si(CH_3)_3$], 18.2 (t, *C*H_2TMS), 69.3 (t, CH_2O), 108.3 (d, C-2), 116.5 (d, C-3), 119.7, 125.4, 125.7, 134.2 (4 d, C-6, C-7, C-8, C-9), 131.6 (s, C-5a), 135.5 (s, C-9b), 145.5 (s, C-1), 162.1 (s, C-5); the signal for C-9a was not detected.

MS (EI, 80 eV, 40 °C): *m*/*z* (%) = 285 (5, [M^+]), 257 (51, [M^+ – C_2H_4]), 242 (14, [M^+ – C_2H_4 – Me]), 214 (13, [M^+ – C_2H_4 – Me – CO]), 130 (13), 102 (14), 73 (100, [TMS^+]), 45 (12, [$C_2H_5O^+$]).

HRMS (EI, 80 eV, 40 °C): *m*/*z* calcd for $C_{16}H_{19}NO_2Si$ [M^+]: 285.1185; found: 285.1174.

Acid-Induced Rearrangement of 7a–c; General Procedure

The allene adduct **7** (1 equiv) was dissolved in THF (7 mL/mmol) and 2 N H_2SO_4 (0.36 mL/mmol) was added. The mixture was stirred for 3 d at r.t. and diluted with H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and worked up to yield the product.

3-(1-Methoxy-2-oxopropylidene)-2,3-dihydro-1*H*-isoindol-1-one (14a)

According to the general procedure, treatment of **7a** (300 mg, 1.38 mmol) with 2 N H_2SO_4 (0.5 mL) in THF (10 mL) yielded after purification by column chromatography (CH_2Cl_2–MeOH, 98:2) 205 mg (68%) of **14a** as pale yellow solid, as a 89:11 mixture of *Z*/*E* diastereomers (determined by ^{1}H NMR spectroscopy); mp 155 °C.

IR (KBr): 3185–2950 (NH, =CH), 1725 (C=O), 1680 (C=C) cm^{-1}.

Major Isomer

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.45 (s, 3 H, CH_3), 3.81 (s, 3 H, OCH_3), 7.51–7.70 (m, 2 H, Ar), 7.88 (d, *J* = 7.3 Hz, 1 H, Ar), 8.61 (br s, 1 H, NH), 8.72 (d, *J* = 7.3 Hz, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 27.9 (q, C-3′), 61.1 (q, OCH_3), 123.6, 126.8, 131.0, 133.2 (4 d, C-4, C-5, C-6, C-7), 124.2 (s, C-3), 125.8 (s, C-1′), 134.5, 137.7 (2 s, C-3a, C-7a), 169.9 (s, C-1), 196.9 (s, C-2′).

MS (EI, 80 eV, 70 °C): *m*/*z* (%) = 217 (100, [M^+]), 202 (38, [M^+ – Me]), 187 (11, [M^+ – 2 Me]), 174 (64, [M^+ – CONH]), 160 (88), 132 (66), 103 (43), 76 (58, [$C_6H_4^+$]), 43 (49).

Anal. Calcd for $C_{12}H_{11}NO_3$ (217.2): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.37; H, 5.02; N, 6.39.

Minor Isomer

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.42 (s, 3 H, CH_3), 7.75, 7.88, 8.05, 8.15 (4 m_c, each 1 H, Ar), 9.90 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 27.1 (q, C-3′), 61.2 (q, OCH_3), 124.1, 125.6, 131.0, 133.0 (4 d, Ar).

3-(1-Benzyloxy-2-oxopropylidene)-2,3-dihydro-1*H*-isoindol-1-one (14b)

According to the general procedure, reaction of **7b** (100 mg, 0.341 mmol) with 2 N H_2SO_4 (0.3 mL) in THF (4 mL) yielded after purification by column chromatography (CH_2Cl_2–MeOH, 98:2) 72 mg (72%) of **14b** as pale yellow solid, as a 88:12 mixture of diastereomers (determined by ^{1}H NMR spectroscopy); melting range 175–180 °C. The ^{13}C NMR signals for the minor isomer are not given, because they could not be assigned unambiguously.

IR (KBr): 3200 (CONH), 3100–2895 (CH), 1720 (C=O), 1680 (C=C) cm^{-1}.

Major Isomer

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.46 (s, 3 H, CH_3), 4.88 (s, 2 H, C*H*$_2$Ph), 7.38–7.46 (m, 5 H, C_6H_5), 7.54–7.58 (m, 1 H, Ar), 7.61–7.66 (m, 1 H, Ar), 7.81–7.84 (m, 2 H, NH, Ar), 8.65–8.69 (m, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 28.8 (q, CH_3), 76.0 (t, *C*H_2Ph), 123.8, 128.4, 129.0, 129.1, 130.9, 130.9, 133.3 (7 d, Ar, C_6H_5), 127.8, 133.6, 134.4, 135.5, 136.3 (5 s, C-3a, C-7a, C-3, C-1′, C_6H_5), 167.7 (s, C-1), 197.7 (s, C-2′).

MS (EI): *m*/*z* (%) = 293 (3, [M^+]), 265 (1, [M^+ – CO]), 250 (1, [M^+ – MeCO]), 221 (36, [M^+ – C_2H_3O – CO]), 202 (14, [M^+ – CH_2Ph]), 173 (34, [M^+ – C_8H_7O]), 160 (34), 102 (23), 91 (100, [$C_7H_7^+$]), 64 (12), 43 (33, [$C_2H_3O^+$]).

HRMS (EI, 80 eV, 150 °C): *m*/*z* calcd for $C_{18}H_{15}NO_3$ [M^+]: 293.1051; found: 293.1058.

Minor Isomer

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.38 (s, 3 H, CH_3), 4.93 (s, 2 H, C*H*$_2$Ph), 7.48 (m_c, 2 H, Ar), 7.88 (m_c, 1 H, Ar), 8.00 (m_c, 1 H, Ar), 9.96 (s, 1 H, NH).

3-{2-Oxo-1-[2-(2-trimethylsilyl)ethoxy]propylidene}-2,3-dihydro-1*H*-isoindol-1-one (14c)

According to the general procedure, treatment of **7c** (70 mg, 0.230 mmol) with 2 N H_2SO_4 (0.3 mL) in THF (4 mL) yielded after column chromatography on silica gel (CH_2Cl_2–MeOH, 99:1) 30 mg (43%) of **14c** as pale yellow solid; mp 168–172 °C.

IR (KBr): 3250 (CONH), 2950–2850 (CH), 1715 (C=O), 1680 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.04 [br s, 9 H, $Si(CH_3)_3$], 1.62 (ddd, *J* = 2.9, 6.5, 8.4 Hz, 2 H, CH_2TMS), 2.43 (s, 3 H, CH_3), 3.92 (ddd, *J* = 2.9, 6.5, 8.4 Hz, 2 H, OCH_2), 7.55 (dt, *J* = 0.8, 7.5 Hz, 1 H, Ar), 7.62 (dt, *J* = 1.3, 7.5 Hz, 1 H, Ar), 7.85 (d, *J* = 7.5 Hz, 1 H, Ar), 8.59 (s, 1 H, NH), 8.64 (d, *J* = 7.5 Hz, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = –1.4 [q, $Si(CH_3)_3$], 19.2 (t, CH_2TMS), 28.1 (q, C-3′), 72.1 (t, OCH_2), 123.6, 130.7, 133.2, 133.7 (4 d, Ar), 126.5, 131.1, 134.0, 136.6 (4 s, C-1′, C-3, C-3a, C-7a), 167.7 (s, C-1), 197.6 (s, C-2′).

MS (EI): *m*/*z* (%) = 303 (1, $[M^+]$), 288 (1, $[M^+ - Me]$), 275 (15, $[M^+ - CO]$), 260 (21, $[M^+ - COMe]$), 231 (36), 73 (100, $[TMS^+]$), 55 (11), 45 (12), 43 (27, $[COMe^+]$), 41 (12).

HRMS (EI, 80 eV, 130 °C): *m*/*z* calcd for $C_{16}H_{21}NO_3Si$ $[M^+]$: 303.1290; found: 303.1285.

3-(1-Methoxy-2-oxopropylidene)-2-methyl-2,3-dihydroisoindol-1-one (15a)

Compound **14a** (120 mg, 0.552 mmol) was dissolved in anhyd acetone (7 mL). Then K_2CO_3 (151 mg, 1.10 mmol) and Me_2SO_4 (78 μL, 1.10 mmol) were added under argon. The solution was stirred for 12 h at r.t. and then for 24 h under reflux. After addition of H_2O (10 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed in vacuo. After purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 99:1) 82 mg (65%) of **15a** was obtained as colorless solid; mp 68–71 °C.

IR (KBr): 3080–3845 (CH), 1750, 1710 (C=O), 1610 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.43 (s, 3 H, CH_3), 3.48 (s, 3 H, NCH_3), 3.66 (s, 3 H, OCH_3), 7.36–7.48 (m, 2 H, Ar), 7.73–7.79 (m, 1 H, Ar), 7.92–7.99 (m, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 28.1 (q, C-3′), 29.7 (q, NCH_3), 60.6 (q, OCH_3), 122.9, 123.8, 129.6, 132.2 (4 d, Ar), 123.8, 129.1, 133.9, 138.7 (4 s, C-1′, C-3, C-3a, C-7a), 129.1 (s, C-3), 167.4 (s, C-1), 198.8 (s, C-2′).

MS (EI, 80 eV, 50 °C): *m*/*z* (%) = 231 (2, $[M^+]$), 216 (1, $[M^+ - Me]$), 205 (24), 161 (100, $[C_{10}H_{11}NO^+]$), 133 (23), 117 (64), 104 (59, $[C_6H_4CO^+]$), 91 (15, $[C_7H_7^+]$), 76 (82, $[C_6H_4^+]$), 49 (54), 43 (37, $[C_2H_3O^+]$), 29 (11).

HRMS (EI, 80 eV, 50 °C): *m*/*z* calcd for $C_{13}H_{13}NO_3$ $[M^+]$: 231.0895; found: 231.1058.

Crystal Structure Data of 15a

Suitable crystals for single X-ray structure determination were obtained by recrystallization of compound **15a** from CH_2Cl_2. The crystallographic data are collected in Table 1. The programs SHELXS97 and SHELXL97 were used for structure solution and refinement.[18,19]

3-(2-Hydroxy-1-methoxypropylidene)-2,3-dihydro-1*H*-isoindol-1-one (16a)

Compound **14a** (65 mg, 0.30 mmol) was dissolved in MeOH (10 mL) under argon and $CeCl_3 \cdot 7H_2O$ (94 mg, 0.30 mmol) was added at r.t. The solution was cooled to 0 °C and $NaBH_4$ (6 mg, 0.16 mmol) was added. The solution was allowed to warm up to r.t. and stirred for 4 h. After addition of H_2O (15 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvents were removed in vacuo. After purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 9:1) 60 mg (92%) of **16a** was obtained as colorless solid; melting range 138–145 °C.

Table 1 Crystallographic Data of **15a**

Empirical formula	$C_{13}H_{13}NO_3$
Fw	231.24
Temperature	173
Wavelength	0.71073
Crystal system, space group	Monoclinic, $P2_1/n$
a (Å)	8.823 (3)
b (Å)	6.674 (2)
c (Å)	19.109 (6)
α (°)	90
β (°)	99.714 (7)
γ (°)	90
Volume	1109.1(6)
Z, calcd density	4
Abs. coeff (1/mm)	0.099
F (000)	488
Crystal size	0.4 × 0.4 × 0.4
θ Range of data collection (°)	2.16 to 30.52
Limiting indices (measured)	h ± 12, k ± 9, l ±27
No. of reflections collected/unique	12695 / 3380
Completeness to θ (%)	99.6
No. of data/parameters	3380 / 0 / 157
Goodness-of-fit on F	1.078
*R*1	0.0496
*wR*2	0.1200

IR (KBr): 3450 (OH), 3170–2930 (C–H), 1710 (C=O), 1660 (C=C) cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.48 (d, *J* = 6.7 Hz, 3 H, 3′-H), 3.93 (s, 3 H, OCH_3), 5.26 (q, *J* = 6.7 Hz, 1 H, 2′-H), 7.43–7.47 (m, 1 H, Ar), 7.59–7.63 (m, 1 H, Ar), 7.78–7.81 (m, 1 H, Ar), 7.84–7.87 (m, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 20.7 (q, C-3′), 61.9 (q, OCH_3), 66.3 (d, C-2′), 124.2, 124.3 (2 d, Ar), 124.4, 131.6, 136.2, 146.2 (4 s, C-7a, C-3a, C-3, C-1′), 129.0, 133.2 (2 d, Ar), 169.0 (s, C=O).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 219 (39, $[M^+]$), 204 (19, $[M^+ - Me]$), 176 (18, $[M^+ - COMe]$), 171 (23), 162 (33), 132 (43), 76 (38, $[C_6H_4^+]$), 69 (30), 43 (63, $[CONH^+]$), 41 (43), 28 (100, $[CO^+]$).

HRMS (EI, 80 eV, 100 °C): *m*/*z* calcd for $C_{12}H_{13}NO_3$ $[M^+]$: 219.0895; found: 219.0887.

(*Z*)- and (*E*)-3-(2-Chloro-1-methoxyprop-2-enylidene)-2,3-dihydro-1*H*-isoindol-1-one (17)

Compound **7a** (200 mg, 0.921 mmol) was partially dissolved in CH_2Cl_2 (6 mL). Then 2 N HCl (1 mL) was added and the mixture was stirred for 2 d at r.t. After addition of H_2O (10 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo. After purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 98:2) 162 mg (75%) of **17** was obtained as pale yellow solid. A mixture of *Z*:*E* isomers in a ratio of 81:19 was obtained. The ratio of the isomers varied in different experiments. The isomers were separated by HPLC (*i*-PrOH–hexane, 15:85).

***Z*-Isomer**

Melting range 135–140 °C.

IR (KBr): 3150–2830 (CONH, CH), 1705 (C=O), 1650 (C=C), 760, 700 (C–Cl) cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.77 (s, 3 H, OCH_3), 5.88, 5.99 (2 d, *J* = 1.4 Hz, each 1 H, 3′-H), 7.38 (dt, *J* = 0.9, 7.5 Hz, 1 H, Ar), 7.45 (dt, *J* = 1.4, 7.5 Hz, 1 H, Ar), 7.83 (m_c, 1 H, Ar), 7.85 (m_c, 1 H, Ar), 8.89 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 56.8 (q, OCH_3), 121.5 (t, C-3′), 121.7, 123.6, 128.1, 131.6 (4 d, Ar), 123.7 (s, C-1′), 130.5, 131.3 (2 s, C-2′, C-3), 135.4, 134.6 (2 s, C-3a, C-7a), 166.7 (s, C-1).

MS (EI, 80 eV, 150 °C): *m*/*z* (%) = 235 (32, [M^+]), 220 (100, [M^+ – Me]), 200 (25, [M^+ – Cl]), 185 (58, [M^+ – Me – Cl]), 156 (21, [M^+ + H – Cl – OMe – CH_2]), 130 (23), 103 (17), 76 (12, [$C_6H_4^+$]).

Anal. Calcd for $C_{12}H_{10}ClNO_2$ (235.2): C, 61.27; H, 4.28; N, 5.98. Found: C, 61.07; H, 4.18; N, 5.58.

***E*-Isomer**

Melting range 150–154 °C.

IR (KBr): 3160–2840 (CONH, CH), 1705 (C=O), 1650 (C=C), 760, 700 (C–Cl) cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.80 (s, 3 H, OCH_3), 5.81, 5.87 (d, t, *J* = 1.4 Hz, each 1 H, 3′-H), 7.48–7.52 (m, 1 H, Ar), 7.60–7.64 (m, 1 H, Ar), 7.87 (d, *J* = 7.5 Hz, 1 H, Ar), 7.94 (s, 1 H, NH), 8.08 (d, *J* = 7.5 Hz, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 125.7 MHz): δ = 58.5 (q, OCH_3), 120.5 (t, C-3′), 123.6, 124.8, 129.1, 132.6 (4 d, Ar), 124.5, 129.6, 131.9 (3 s, C-1′, C-2′, C-3), 134.2, 135.7 (2 s, C-3a, C-7a), 167.2 (s, C-1).

MS (EI, 80 eV, 60 °C): *m*/*z* (%) = 235 (100, [M^+]), 220 (76, [M^+ – Me]), 200 (22, [M^+ – Cl]), 185 (47, [M^+ – Me – Cl]), 156 (17, [M^+ + H – Cl – OMe – CH_2]), 130 (28), 103 (33), 76 (34, [$C_6H_4^+$]), 28 (13, [CO^+]).

Anal. Calcd for $C_{12}H_{10}ClNO_2$ (235.2): C, 61.27; H, 4.28; N, 5.98. Found: C, 61.17; H, 4.34; N, 5.64.

Acknowledgment

The authors thank the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and Schering AG for financial support of this research. We thank Dr. R. Zimmer for his assistance during the preparation of this manuscript.

References

(1) (a) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609. (b) Hormuth, S.; Reissig, H.-U. *Synlett* **1991**, 179. (c) Hormuth, S.; Reissig, H.-U. *J. Org. Chem.* **1994**, *59*, 67. (d) Hormuth, S.; Schade, W.; Reissig, H.-U. *Liebigs Ann. Chem.* **1996**, 2001.

(2) Okala Amombo, G. M.; Hausherr, A.; Reissig, H.-U. *Synlett* **1999**, 1871.

(3) (a) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632. (b) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fisera, L.; Hlobilova, I.; Zahn, G.; Reissig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003.

(4) (a) Reissig, H.-U.; Hormuth, S.; Schade, W.; Okala Amombo, G. M.; Watanabe, T.; Pulz, R.; Hausherr, A.; Zimmer, R. *Lectures in Heterocyclic Chemistry Vol. XVI,* In *J. Heterocycl. Chem.* **2000**, *37*, 597. (b) Reissig, H.-U.; Schade, W.; Okala Amombo, G. M.; Pulz, R.; Hausherr, A. *Pure Appl. Chem.* **2002**, *74*, 175.

(5) (a) Zimmer, R. *Synthesis* **1993**, 165. (b) Zimmer, R.; Reissig, H.-U. *Donor-Substituted Allenes,* In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, **2004**, Chap. 8, 425.

(6) (a) Hausherr, A. *Ph.D. Dissertation*; Freie Universität Berlin: Germany, **2001**. (b) Flögel, O.; Okala Amombo, G. M.; Reissig, H.-U.; Zahn, G.; Brüdgam, I.; Hartl, H. *Chem. Eur. J.* **2003**, *9*, 1405. (c) Kaden, S.; Brockmann, M.; Reissig, H.-U. *Helv. Chim. Acta* **2005**, *88*, 1826.

(7) Al-Harrasi, A.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2005**, *44*, 6227; *Angew. Chem.* **2005**, *117*, 6383.

(8) Honma, T.; Hayashi, K.; Aoyama, T.; Hashimoto, N.; Machida, T.; Fukasawa, K.; Iwama, T.; Ikeura, C.; Suzuki-Takahashi, I.; Iwasawa, Y.; Hayama, T.; Nishimura, S.; Morishima, H. *J. Med. Chem.* **2001**, *44*, 4615.

(9) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.

(10) (a) Itahara, T. *J. Chem. Soc., Chem. Commun.* **1981**, 254. For photoinduced cyclizations, see also: (b) Schmickler, H.; Bartoschek, A.; Kramer, W.; Griesbeck, A. G. *Org. Lett.* **2001**, *3*, 537.

(11) Wang, E.-C.; Chen, H.-F.; Feng, P.-K.; Lin, Y.-L.; Hsu, M.-K. *Tetrahedron Lett.* **2002**, *43*, 9163.

(12) (a) Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand. Ser. B* **1979**, *33*, 309. (b) Robinson, E. D.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 3450. (c) Bartley, G. S.; Marshall, J. A. *J. Org. Chem.* **1994**, *59*, 7169.

(13) Okala Amombo, G. M. *Ph.D. Dissertation*; Technische Universität Dresden: Germany, **2000**.

(14) (a) Frost, T. M.; Choi, J.-H.; Schwarz, L.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; *Angew. Chem.* **2000**, *112*, 2382. (b) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129. For reviews see: (c) Dyker, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4237; *Angew. Chem.* **2000**, *112*, 4407. (d) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (e) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431.

(15) (a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (b) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (c) See also: Lee, P. H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Kim, H.; Seomon, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 1840; *Angew. Chem.* **2005**, *117*, 1874.

(16) Flögel, O.; Dash, J.; Brüdgam, I.; Hartl, H.; Reissig, H.-U. *Chem. Eur. J.* **2004**, *10*, 4283.

(17) (a) Reppe, W. *Liebigs Ann. Chem.* **1955**, *596*, 1. (b) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1985**, *50*, 5308.

(18) Sheldrick, G. M. *SHELX97 (includes SHELXS97, SHELXL97, and CIFTAB) Programs for Crystal Structure Analysis (Release 97-2)*; Universität Göttingen: Germany, **1998**.

(19) Crystallographic data for **15a** can be obtained from Cambridge Crystallographic Data Centre, CCDC reference number: 286363.