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Regiodivergent Stereoselective Access to Fused Alkylideneazetidines

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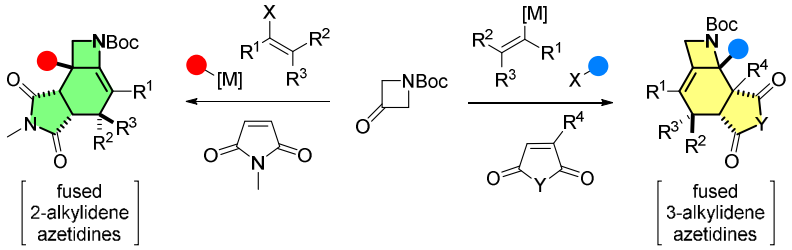
Supporting Information Placeholder



ABSTRACT: Following recent advances on the generalization and simplification of 2*H*-azetine synthesis, a regiodivergent approach to fused 2-, and 3-alkylideneazetines was designed via the intermediate formation of unprecedented vinylazetine structures. Concise sequences to the latter are described, from which expected unsaturated fused ring system were isolated with very high yields, regio- and stereoselectivities by [4+2]-cycloadditions.

Introduction

Nitrogen-containing heterocycles are essential motifs in organic and medicinal chemistry[1] as their incorporation in drugs has been leading a number of synthetic studies.[2] As β-lactams have become important in pharmacology after the discovery of penicillin, a part of medicinal chemistry research has been dedicated to exploring the synthesis and biological activities of such strained four-membered heterocycles. More than antibiotic properties, azetidine-derived fused systems present a wide range of applicability, showing for example anti-viral and antifungal activities (Figure 1).[3-5]

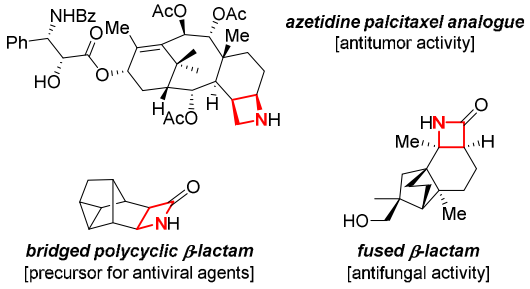
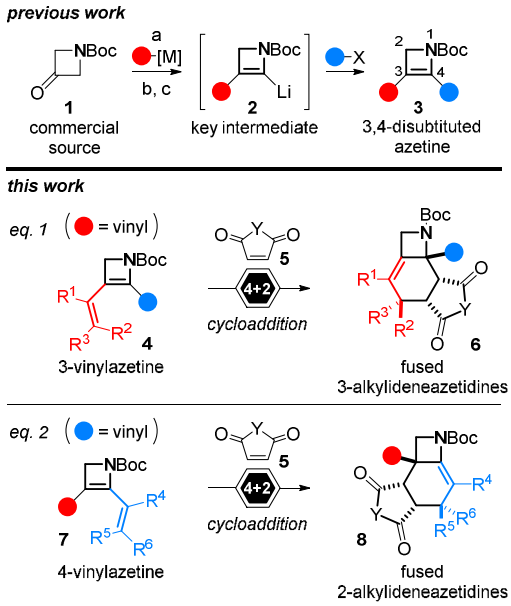


Figure 1. Selected examples of fused *N*-containing four-membered rings.

Moreover, a relatively restrained library of fused azetidines found in the literature points out the importance of these motifs as potential candidates for the treatment of a variety of diseases, including antitumor agents.[6] While smaller and larger *N*-containing heterocycles have been intensively studied, the general formation of azetines[7] and alkylideneazetines[8] remains a challenge in organic chemistry.

Scheme 1. Past and present work on the formation of unsaturated four-membered *N*-heterocycles.



a) organolithium (M = Li) or organomagnesium (M = MgBr) were employed (1.2 eq.); reactions were performed in THF at -30 °C. b) NaH, MeI, THF, 0°C to rt. c) s-BuLi (2 eq.), TMEDA (1 eq.), THF, -78 °C.

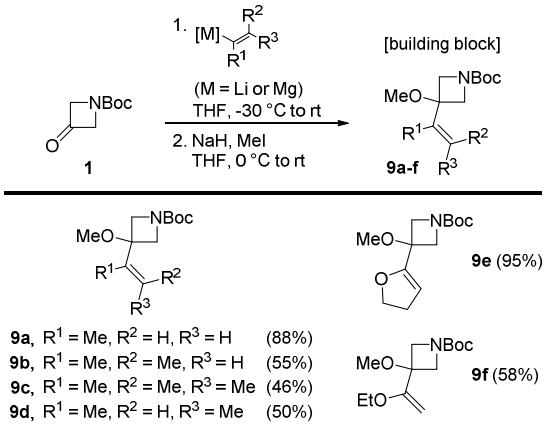
En route to developing new accesses to sophisticated azetidine structures, we recently generalized the synthesis of 3,4-disubstituted 2-azetines **3** through the key formation of an azetinyllithium intermediate **2** (Scheme 1).[9] While direct electrophilic trapping furnished alkylated, silylated and carbinol derivatives, transmetalation to boron followed by in-situ Su-

zuki coupling opened an unprecedented access to 4-arylated derivatives. Importantly, desired structures could be obtained in only three steps and after a sole purification. Starting from a commercial source of 3-azetidinone **1**,[10] the introduction of the substituent at position 3 can be simply done by nucleophilic 1,2-addition of an organometallic and subsequent methylation of the resulting tertiary alcohol giving then adequate substrates for the double α-lithiation / trapping sequence pioneered by Hodgson.[9,11] Employing either vinylmetal species (eq. 1) or performing the subsequent cross-coupling with vinyl halides (eq. 2) respectively furnishes 3-, and 2-vinylazetines **4** and **7** (Scheme 1). Upon addition of a dienophile **5**, a stereoselective [4+2]-cycloaddition takes place, leading to fused alkylideneazetidines (AAz) **6** and **8**. The regiodivergence of the strategy simply comes from the nature of the embedded diene initially employed (3-vinylazetine **4** or 4-vinylazetine **7**).

Results and Discussion

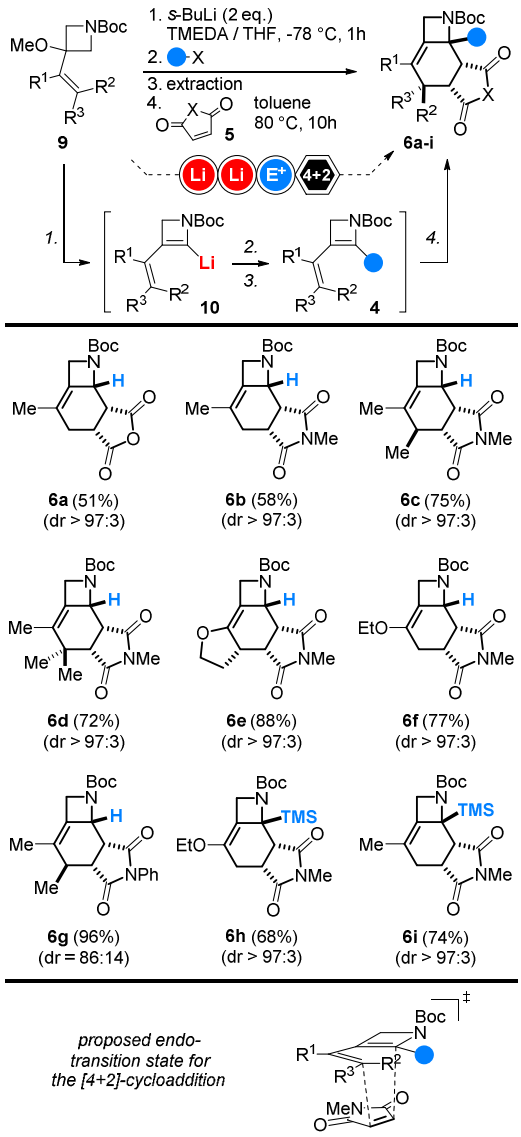
In Scheme 2, we detail the two-step preparation of 3-vinylazetidine building blocks **9a-f**.[12,13] Upon addition of an alkenylmetal species on **1**, tertiary alcohols are intermediary formed and further methylated without need for purification. Diverse alkenyl groups and vinylethers[13] were introduced, giving access to the desired substrates **9a-f** in moderate to high yields (46 to 95%).

Scheme 2. Preparation of 3-vinylazetidine building blocks.



Starting from these vinylazetidines **9a-f**, α-lithiation in the presence of *s*-BuLi promotes a β-elimination and an excess amount of *s*-BuLi yields the key azetinyllithium intermediate **10** that can then be trapped by the appropriate electrophile (H_2O or TMSCl, Scheme 3).[12] Resulting dienes **4** were subsequently engaged in a [4+2]-cycloaddition with electron deficient dienophiles **5** to afford fused AAz **6a-i** with excellent control over the stereochemical outcome of the transformation in all cases (dr = 97:3).[14] While isopropenylmetal species (R^1 = Me) led to **6a** and **6b** with good yields employing respectively maleic anhydride or *N*-methylmaleimide, the possibility of adding a stereocenter was explored by using an in-situ generated *trans*-2-butenyllithium as the starting organometallic species. **6c** and **6g** (from *N*-phenylmaleimide) containing four consecutive stereocenters were obtained with an excellent diastereomeric ratio and up to 96% yield. A decrease in stereoselectivity was however observed when employing *N*-phenylmaleimide (**6g**, dr = 86:14). Interestingly, bulky substrates also furnished expected product **6d** in good yields. Using Feringa's deprotonation for the formation of lithiated vinyl ether[13] resulted in the formation of tetracyclic AAz **6e** and *O*-ethyl substituted AAz **6f** in 77 to 88% yield. Following the double deprotonation, subsequent addition of TMSCl in the formation of **4** led to quaternary stereocenter containing AAz **6h** and **6i** in good yields and stereoselectivities.[15]

Scheme 3. Three-step sequence towards fused AAz.[a]

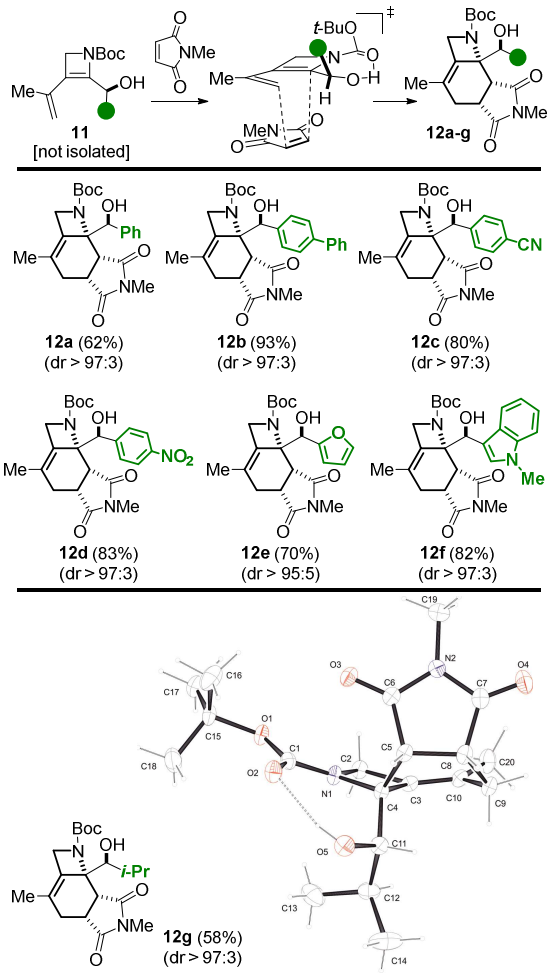


[a] Indicated yields are calculated from compound **9** after the three-step sequence, including the extraction step, see supporting information.

With an efficient ex-situ preparation of functionalized dienes embedded in the azetine structures in hands, we envisioned that a chiral substrate **11** (Scheme 4) – obtained by intermediate addition of an aldehyde – could lead to a diastereocontrolled [4+2]-cycloaddition. Benzaldehyde was first used on 4-azetinyllithium species, furnishing the corresponding azetine carbinol **11a** which was engaged crude in the cycloaddition with *N*-methylmaleimide. Delightfully, **12a** was isolated in good yields and with an excellent diastereomeric

ratio (dr = 97:3). We propose to explain this exceptional stereoselectivity by an intramolecular H-bonding between the hydroxyl moiety and the Boc group, placing the aromatic group – coming initially from the aldehyde – on one of the two diastereotopic faces. Potential allylic strain reinforces this selectivity, placing the larger group (aromatic) out of the plane. As a result, the dienophile preferentially approaches from the less hindered face of the diene. X-ray measurements on product **12g** showed a H-bonding and we assume that this interaction plays a determining role in the diastereoselectivity of the reaction, as proposed in the transition state (Scheme 4).[16] Aromatic as well as heteroaromatic substrates furnished **12b-d** and **12e,f**, respectively, with similarly high yields and diastereoselectivities.

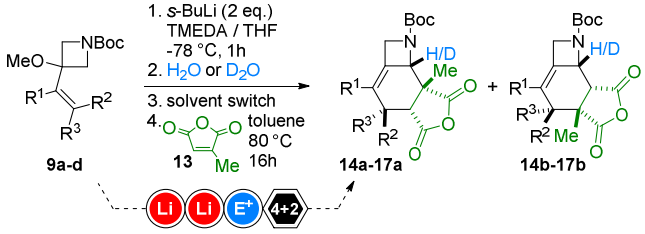
Scheme 4. Diastereoselective approach toward AAz.[a]



[a] Indicated yields are calculated from compound **9** after the three-step sequence, including the extraction step, see supporting information.

In order to introduce a quaternary stereocenter α to a carbonyl position, we next employed citraconic anhydride **13** as dienophile. Dienes **4g-i** and **4l** obtained after quenching with either H_2O or D_2O were employed without further purification. Interestingly, different regioselectivities were observed depending on the bulkiness of the diene engaged in the cycloaddition reaction (Scheme 5). While the less bulky terminal diene (from **9a**) only gave moderate regioselectivities (**14a**:**14b** = 75:25), the most substituted one (from **9c**) furnished exclusively **17a** in 89% yield

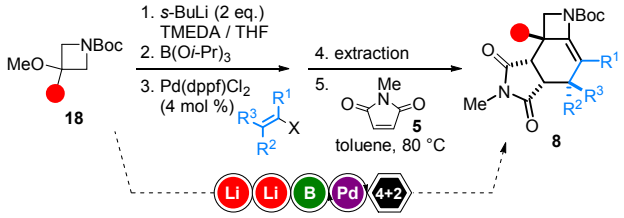
Scheme 5. Synthesis of AAz using 3-methylfuran-2,5-dione.[a]

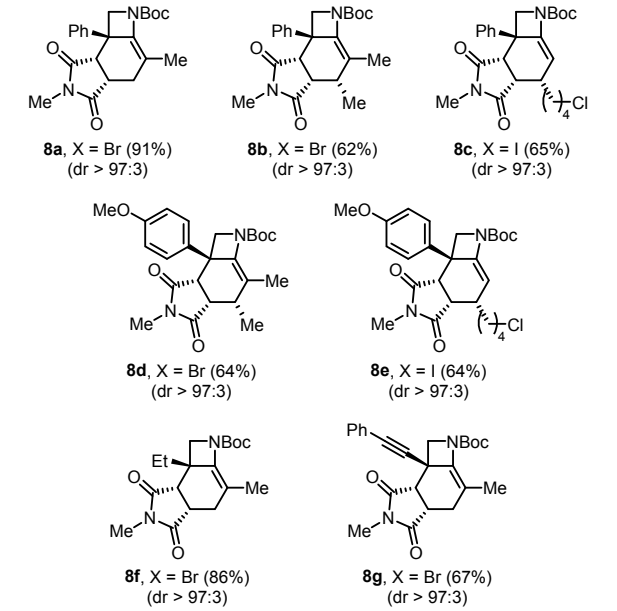


from **9a**	**14** (D), R^1 = Me, R^2 = H, R^3 = H	(54%)	(**14a**:**14b** = 75:25)
from **9d**	**15** (H), R^1 = Me, R^2 = H, R^3 = Me	(45%)	(**15a**:**15b** = 79:21)
from **9b**	**16** (D), R^1 = Me, R^2 = Me, R^3 = H	(62%)	(**16a**:**16b** = 83:17)
from **9c**	**17** (H), R^1 = Me, R^2 = Me, R^3 = Me	(89%)	(**17a**:**17b** = 100:0)

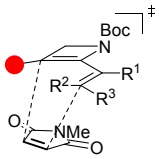
[a] Indicated yields are calculated from compound **9** after the three-step sequence, including the extraction step, see supporting information.

Scheme 6. Access to fused 2-alkylideneazetidines.[a]





proposed endo-transition state for the [4+2]-cycloaddition



[a] Indicated yields are calculated from compound **9** after the three-step sequence, including the extraction step, see supporting information.

As this variable regioselectivity can be easily explained by steric repulsion between the methyl group of the dienophile and the substituents at the vinylic position, *cis*-, and *trans*-dimethylvinyl substrates (respectively from **9d** and **9b)** led to intermediate regioselectivities (79:21 and 83:17, respectively). Importantly, regioisomers could be isolated separately via chromatography.

Finally, a regiodivergent approach toward fused 2-AAz was designed starting form aryl, alkyl and alkynyl-substituted azetidines **18** (Scheme 6). Following the above-described lithiation sequence led to the corresponding azetinylboronate upon addition of boron isopropoxide. Subsequent addition of vinyl iodide or bromide furnished dienes **7** (not depicted in Scheme 6) through an in-situ Suzuki cross-coupling catalyzed by $Pd(dppf)Cl_2 \cdot CH_2Cl_2$. These 4-vinylazetines were then directly engaged in the Diels-Alder cycloaddition with *N*-methylmaleimide **5** without further purification, but after extracting switching the solvent to toluene. In all cases, a perfect control over the diastereoselective outcome was achieved (dr > 97:3). 3-aryl, alkyl and alkynyl substituted substrates led to fused ring systems **8a-g** in good to excellent yields (up to 91%) containing up to four consecutive stereocenters.

Conclusion

In conclusion, we assembled highly stereoselective three-step sequences in which successive α-metallation, electrophilic addition and [4+2]-cycloaddition led to unprecedented fused tri- and tetracyclic alkylideneazetidines with up to four consecutive stereocenters. Both regioisomers could be accessed independently through this simple and efficient strategy, taking advantage of an easy and straightforward substrate preparation. Paths allowing the formation of these interesting patterns surely represent important advances in the chemistry of nitrogen-containing four-membered rings and their potential implications in drug-discovery processes.

Experimental Section

General considerations. Commercially available starting materials were used without further purification unless otherwise stated. All reactions were carried out under N_2 atmosphere in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with nitrogen prior to use. CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen. Et_2O was predried over $CaCl_2$ and passed through activated Al_2O_3 (the solvent purification system SPS-400-2 from Innovative Technologies Inc.). Toluene was predried over $CaCl_2$ and distilled from, CaH_2. Chromatography purifications were performed using silica gel (SiO_2, 0.040-0.063 mm, 230-400 mesh ASTM) from Merck. The spots were visualized under UV (254 nm) or by staining the TLC plate with $KMnO_4$ solution (K_2CO_3, 10 g – $KMnO_4$, 1.5 g – H_2O, 150 mL – NaOH 10% in H_2O, 1.25 mL), *p*-anisaldehyde solution (conc. H_2SO_4, 10 mL – EtOH, 200 mL – AcOH, 3 mL – *p*-anisaldehyde, 4 mL). Diastereoisomeric ratios were determined by ^{1}H NMR and ^{13}C NMR. ^{13}C and ^{1}H NMR spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ values in ppm relative to residual solvent peak (^{1}H-NMR) or solvent peak (^{13}C-NMR) in deuterated chloroform ($CDCl_3$: δ 7.26 ppm for ^{1}H-NMR and δ 77.16 ppm for ^{13}C-NMR). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broad). Reaction endpoints were determined by GC monitoring of the reactions. Gas chromatography was performed with machines of Agilent Technologies 7890, using a column of type HP 5 (Agilent 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 μm) or Hewlett-Packard 6890 or 5890 series II, using a column of type HP 5 (HewlettPackard, 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0,25 mm; film thickness: 0.25 μm). High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument or JEOL JMS-700. Infrared spectra were recorded on a Perkin 281 IR spectrometer and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bands were reported in wave numbers (cm-1) and abbreviations for intensity are as follows: vs (very strong; maximum intensity), s (strong; above 75% of max. intensity), m (medium; from 50% to 75% of max. intensity), w (weak; below 50% of max. intensity) and br (broad). Melting points were determined on a Büchi B-540 apparatus and uncorrected. Single crystals were grown in small quench vials with a volume of 5.0 mL from slow evaporation of dichloromethane/hexanes mixtures at room temperature. Suitable single crystals were then introduced into perfluorinated oil and mounted on top of a thin glass wire. Data collection was performed at 100 K with a Bruker D8 Venture TXS equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector operating with Mo-Kα radiation (l = 0.71071 Å).

s-BuLi and *t*-BuLi were purchased as solutions in cyclohexane/hexanes mixtures from Rockwood Lithium GmbH. The commercially available Grignard reagents MeMgCl, PhMgCl and *n*-BuMgCl were also purchased from Rockwood Lithium GmbH, as solutions in THF.

The concentration of organometallic reagent from commercially purchased and synthesized reagents was determined either by titration of isopropyl alcohol using the indicator 4-(phenylazo)diphenylamine in THF for Grignard reagents or using the indicator N-benzylbenzamide in THF for organolithium reagents.

[*s*-BuLi] = 1.31 M in cyclohexane (titration with isopropanol / 1,10-phenanthroline), purchased from Rockwood Lithium GmbH.
[*t*-BuLi] = 2.00 M in hexane (titration with isopropanol / 1,10-phenanthroline), purchased from Rockwood Lithium GmbH.

General procedure A for the synthesis of organomagnesium-vinyl reagents:[13]
In a Schlenk flask, two equivalents of magnesium turnings were layered with either diethyl ether or THF. One seed of iodine was added for activation and one drop of concentrated corresponding vinylbromide was added. After ensuring that the reaction had started, the corresponding bromides were solubilised in the appropriate solvent and added dropwise at a constant rate that would keep the reaction constantly refluxing. After completed addition, the reaction was stirred for three more hours at room temperature and the organomagnesium reagents stored under nitrogen.

General procedure B for the synthesis of 3-substituted 1-Boc-3-methoxyazetidines (**9a-f**, **18a-d**): Commercially available *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) (1.0 eq., 5.0 mmol) was dissolved in THF (20 mL) and cooled to -30 °C. The corresponding vinyl-Grignard (1.3 eq., 6.5 mmol) or vinyllithium species[13] was added dropwise and the solution stirred for one hour before warming to room temperature. The reaction mixture was quenched with saturated NH_4Cl and extracted twice with diethyl

ether (2x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under vacuum. The crude alcohol was then redissolved in THF (10 mL) and cooled to 0 °C. After adding sodium hydride (1.3 eq., 6.5 mmol) portion-wise, the reaction mixture was allowed to reach room temperature and stirred for one hour. Methyl iodide (1.3 eq., 6.5 mmol) was then added and the mixture stirred for two more hours at room temperature. The reaction was quenched with methanol and the solvents were evaporated. Purification by column chromatography on silica gel gave substituted 3-substituted 1-boc-3-methoxyazetidines **9a-f**.

General procedure C for the synthesis of alkylideneazetidines (**6a-i**/**12a-g**): Azetidines **9a-f** (0.50 mmol, 1.0 eq.) were dissolved in THF (5.0 mL) and the solution was cooled down to -78 °C. After the addition of TMEDA (1.3 mmol, 2.5 eq.), *s*-BuLi (1.3 mmol, 1.31 M, 2.5 eq.) was added dropwise and the mixture stirred for one hour. The reaction was then quenched with the corresponding electrophile (H_2O, TMSCl, D_2O, aldehydes), stirred for 30 minutes and warmed up to room temperature. After workup with saturated NH_4Cl and extraction with diethyl ether (2x 10 mL), the organic phases were combined and dried over Na_2SO_4. The crude dienes were then redissolved in toluene (3.0 mL) and transferred into a pressure tube. The dienophile was added (1.0 mmol, 2.0 eq.) and the sealed pressure tube was heated between 80 °C for 10 -24 h. Evaporation of the solvent and purification by column chromatography led to compounds **6a-i**/**12a-g**.

General procedure D for the synthesis of alkylideneazetidines (**14a-17a**/**14b-17b**): Azetidines **9a-d** (0.50 mmol, 1.0 eq.) were dissolved in THF (5.0 mL) and the solution was cooled down to -78 °C. After the addition of TMEDA (1.3 mmol, 2.5 eq.), *s*-BuLi (1.3 mmol, 1.31 M, 2.5 eq.) was added dropwise and the mixture stirred for one hour. The reaction was then quenched with the corresponding electrophile (H_2O or D_2O), stirred for 30 minutes and warmed up to room temperature. After workup with saturated NH_4Cl and extraction with diethyl ether (2x 10 mL), the organic phases were combined and dried over Na_2SO_4. The crude dienes were then redissolved in toluene (3.0 mL) and transferred into a pressure tube. The dienophile was added (1.0 mmol, 2.0 eq.) and the sealed pressure tube was heated between 80 °C for 16 h. Evaporation of the solvent and purification by column chromatography led to compounds **14a-17a**/**14b-17b**.

General procedure E for the synthesis of alkylideneazetidines (**8a-g**): Azetidines (0.50 mmol, 1.0 eq.) were dissolved in THF (5.0 mL) and the solution was cooled down to -78 °C. After the addition of TMEDA (1.3 mmol, 2.5 eq.), *s*-BuLi (1.3 mmol, 1.31 M, 2.5 eq.) was added dropwise and the mixture stirred for one hour. The reaction was then quenched with 2.0 eq $B(O\textit{i}\text{-}Pr)_3$, stirred for 60 minutes at 0 °C. After this time, $Pd(dppf)Cl_2$.DCM (4 mol%) as well as the corresponding vinyl-halogenide (X = I or Br) was added and let stirr for 24 h. After workup with saturated NH_4Cl and extraction with diethyl ether (2x 10 mL), the organic phases were combined and dried over Na_2SO_4. The crude dienes were then redissolved in toluene (3.0 mL) and transferred into a pressure tube. The dienophile was added (1.0 mmol, 2.0 eq.) and the sealed pressure tube was heated between 80 °C for 10 -24 h. Evaporation of the solvent and purification by column chromatography led to compounds **8a-g**.

Experimental Data

***tert*-Butyl-3-methoxy-3-(prop-1-en-2-yl)azetidine-1-carboxylate** (**9a**): Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and isopropenylmagnesium bromide according to general procedure **B**, provided **9a** (4.40 mmol, 1.00 g, 88%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 5.04 (s, 1H), 3.97 (d, J = 9.0 Hz, 2H), 3.85 (d, J = 9.1 Hz, 2H), 3.06 (s, 3H), 1.67 (s, 3H), 1.44 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 142.0, 114.9, 79.7, 77.8, 58.3, 56.3, 51.0, 28.5, 17.2 ppm. LRMS (ESI-quadrupole pos): m/z (%): 212.1 (1), 170.1 (32), 154.1 (8). HRMS (ESI-quadrupole pos): calcd for $C_{11}H_{18}NO_3^+$: 212.1287; found: 212.1301. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2946 (w), 2884 (w), 2826 (vw), 1704 cm^{-1} (vs).

***tert*-Butyl-(*Z*)-3-(but-2-en-2-yl)-3-methoxyazetidine-1-carboxylate** (**9b**): Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure **B**, provided **9b** after purification on silica gel (hexane/ethyl acetate 9:1), (3.70 mmol, 900 mg, 55%) as a colourless crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (q, J = 7.2, 6.8 Hz, 1H), 4.02 (d, J = 9.3 Hz, 2H), 3.92 (d, J = 9.3 Hz, 2H), 3.14 (s, 3H), 1.66 (s, 3H), 1.57 (d, J = 7.2 Hz, 3H), 1.42 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 132.0, 126.7, 79.6, 76.8, 58.6, 50.8, 28.5, 21.2, 14.7 ppm. LRMS (ESI-quadrupole pos): m/z (%): 184.1 (16), 168.1 (6), 153.1 (4), 112.1 (68). HRMS (ESI-quadrupole pos): calcd for $C_9H_{14}NO_3^+$ [M-*t*-Bu]$^+$: 184.0974; found: 184.0984. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2944 (w), 2884 (w), 2824 (vw), 1694 cm^{-1} (vs).

***tert*-Butyl-3-methoxy-3-(3-methylbut-2-en-2-yl)azetidine-1-carboxylate** (**9c**): Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure **B**, provided **9c** after purification on silica gel (hexane/ethyl acetate 9:1), (3.00 mmol, 760 mg, 46%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (d, J = 9.4 Hz, 2H), 3.92 (d, J = 9.4 Hz, 2H), 3.14 (s, 3H), 1.71 (s, 3H), 1.61 (d, J = 6.4 Hz, 6H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 133.1, 124.9, 79.6, 78.3, 58.9, 50.9, 28.5, 21.6, 16.5 ppm. LRMS (ESI-quadrupole pos): m/z (%): 198.2 (9), 184.2 (3). HRMS (ESI-quadrupole pos): calcd for $C_{10}H_{16}NO_3^+$ [M-*t*-Bu]$^+$: 198.1130; found: 198.1123. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2942 (w), 2880 (w), 2822 (vw), 2244 (vw), 1704 cm^{-1} (vs).

***tert*-Butyl-(*E*)-3-(but-2-en-2-yl)-3-methoxyazetidine-1-carboxylate** (**9d**): Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure **B**, provided **9d** after purification on silica gel (hexane/ethyl acetate 9:1), (2.00 mmol, 482 mg, 50%) as colorless oil. Rf = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 – 5.53 (m, 1H), 3.99 – 3.91 (m, 2H), 3.81 (d, J = 9.0 Hz, 2H), 3.01 (s, 3H), 1.68 (d, J = 7.5 Hz, 3H), 1.53 (s, 3H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 132.5, 123.7, 79.6, 78.9, 50.7, 28.5, 13.4, 11.0 ppm. LRMS (ESI-quadrupole pos): m/z (%): 242.2 (40), 227.1 (35), 186.1 (60), 154.0 (5). HRMS (ESI-quadrupole pos): calcd for $C_{13}H_{24}NO_3^+$: 242.1751, found 242.1751. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2934 (w), 2882 (w), 2824 (vw), 1702 cm^{-1} (vs).

***tert*-Butyl-3-(4,5-dihydrofuran-2-yl)-3-methoxyazetidine-1-carboxylate** (**9e**): Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure **B**, provided **9e** after purification on silica gel (hexane/ethyl acetate 9:1), (3.80 mmol, 980 mg, 95%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (t, J = 2.5 Hz, 1H), 4.41 (t, J = 9.4 Hz, 2H), 3.98 (d, J = 0.8 Hz, 2H), 3.93 (d, J = 9.6 Hz, 2H), 3.21 (s, 3H), 2.71 (td, J = 9.4, 2.5 Hz, 2H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 155.4, 99.7, 79.8, 72.0, 70.8, 58.6, 57.3, 52.1, 30.2, 28.5 ppm. LRMS (ESI-quadrupole pos): m/z (%): 198.1 (16), 182.1 (6), 154.1 (5), 126.1 (75), 96.1 (44), 85.1 (11), 67.1 (9), 57.1 (100). HRMS (ESI-quadrupole pos): calcd for C $C_9H_{12}NO_4^+$ [M-*t*-Bu]$^+$: 198.0766; found: 198.0754. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (m), 2884 (w), 2836 (vw), 1702 cm^{-1} (vs).

***tert*-Butyl 3-(1-ethoxyvinyl)-3-methoxyazetidine-1-carboxylate** (**9f**): Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and vinyllithium according to general procedure **B**, provided **9f** after purification on silica gel (hexane/ethyl acetate 9:1), (2.33 mmol, 600 mg, 58%) as colorless oil. Rf = 0.5 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 – 4.22 (m, 2H), 4.05 (d, J = 9.2 Hz, 2H), 3.89 (d, J = 9.2 Hz, 2H), 3.79 (q, J = 7.0 Hz, 2H), 3.21 (s, 3H), 1.44 (s, 9H), 1.33 ppm (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 156.6, 84.3, 79.7, 76.0, 63.5, 51.8, 28.5, 28.5, 14.5 ppm. LRMS (ESI-quadrupole pos): m/z (%): 258.2 (100), 202.1 (50), 170.1 (10), 126.6 (2). HRMS (ESI-quadrupole pos): calcd for $C_{13}H_{24}NO_4^+$: 258.1700, found 258.1702. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2934 (w), 2886 (w), 1704 (vs), 1628 cm^{-1} (w).

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-3-methyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate** (**6a**): Using *tert*-butyl 3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and maleic anhydride according to general procedure **C**, provided **6a** (0.20 mmol, 60 mg, 51%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, J = 9.4 Hz, 1H), 4.55 (d, J = 11.3 Hz, 1H), 4.33 (d, J = 12.2 Hz, 1H), 3.71 (t, J = 8.5 Hz, 1H), 3.41 (ddd, J = 8.9, 5.5, 1.9 Hz, 1H), 2.60 (dd, J = 15.2, 1.9 Hz, 1H), 2.25 (d, J = 16.1 Hz, 1H), 1.71 (s, 3H), 1.49 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 167.8, 136.6, 127.8, 125.7, 80.9, 77.2, 62.6, 56.4, 43.1, 42.2, 29.0, 28.4, 18.5 ppm. LRMS (DEP/EI-Orbitrap): m/z 293.3 (2), 237.2 (4), 195.2 (9). HRMS (EI-Orbitrap): calcd for $C_{15}H_{19}NO_5^+$: 293.1263; found: 293.1255. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2984 (w), 2933 (w), 2869 (vw), 1837 (w), 1773 (s), 1685 (vs), 1645 cm^{-1} (w). mp (°C): 170 – 175.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**6b**): Using *tert*-butyl 3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1H-pyrrole-2,5-dione according to general procedure **C**, provided **6b** (0.23 mmol, 70 mg, 58%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, J = 9.1 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.23 (d, J = 12.2 Hz, 1H), 3.44 (t, J = 8.5 Hz, 1H), 3.06 (t, J = 8.5 Hz, 1H), 2.96 (s, 3H), 2.60 (dd, J = 15.1, 1.5 Hz, 1H), 2.17 (d, J = 15.6 Hz, 1H), 1.64 (s, 3H), 1.51 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 174.5, 156.7, 126.7, 125.2, 77.2, 63.9, 55.6, 42.1, 41.2, 28.8, 28.5, 25.4, 18.4 ppm. LRMS (DEP/EI-Orbitrap): m/z 306.1 (1), 250.1 (31), 233.1 (8), 206.1 (38), 191.0 (11). HRMS (EI-Orbitrap): calcd for $C_{16}H_{22}N_2O_4^+$: 306.1580; found: 306.1588. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2972 (w), 2944 (w), 2926 (w), 2881 (w), 2866 (w), 1776 (w), 1698 cm^{-1} (vs). mp(°C): 110 – 115.

***tert*-Butyl-(4*R**,4a*R**,7a*R**,7b*R**)-3,4,6-trimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**6c**): Using *tert*-butyl (*Z*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **6c** (0.38 mmol, 120 mg, 75%) as a sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (dq, J = 9.5, 2.3 Hz, 1H), 4.53 – 4.42 (m, 1H), 4.18 (ddd, J = 12.0, 2.7, 1.2 Hz, 1H), 3.45 (t, J = 8.9 Hz, 1H), 2.93 (s, 3H), 2.88 (ddd, J = 11.9, 7.6, 1.7 Hz, 2H), 1.62 (q, J = 1.8 Hz, 3H), 1.49 (s, 9H), 1.08 ppm (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 174.2, 157.2, 132.3, 123.9, 80.4, 63.2, 56.4, 48.4, 42.3, 36.2, 28.4, 25.3, 18.7, 17.6 ppm. LRMS (DEP/EI-Orbitrap): m/z 264.1 (29), 247.2 (9), 220.2 (40), 205.1 (27), 153.1 (45). HRMS (EI-Orbitrap): calcd for $C_{17}H_{24}N_2O_4^+$: 320.1736; found: 320.1730. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2970 (w), 2932 (w), 2872 (vw), 1778 (w), 1694 cm^{-1} (vs).

***tert*-Butyl-(4a*S**,7a*R**,7b*R**)-3,4,4,6-tetramethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**6d**): Using *tert*-butyl 3-(3-methylbut-2-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **6d** (0.36 mmol, 120 mg, 72%) as a yellow sticky foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (dq, J = 9.9, 2.4 Hz, 1H), 4.40 (dt, J = 11.8, 2.1 Hz, 1H), 4.12 – 4.05 (m, 1H), 3.42 (dd, J = 9.7, 7.9 Hz, 1H), 2.85 (s, 3H), 2.67 (d, J = 7.7 Hz, 1H), 1.56 (d, J = 1.4 Hz, 3H), 1.51 (s, 3H), 1.44 (s, 9H), 0.99 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 173.6, 157.8, 135.6, 124.4, 80.4, 77.2, 63.9, 56.3, 54.2, 43.6, 37.8, 28.5, 28.2, 24.8, 24.2, 14.1 ppm. LRMS (DEP/EI-Orbitrap): m/z 278.1 (16), 261.1 (9), 234.2 (20), 219.2 (52), 202.1 (5), 167.1 (92). HRMS (EI-Orbitrap): calcd for $C_{18}H_{26}N_2O_4^+$: 334.1893; found: 334.1895. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2934 (vw), 2872 (vw), 2254 (vw), 1778 (w), 1696 cm^{-1} (s).

tert-Butyl-(5aS,5bR,8aR,8bR)-7-methyl-6,8-dioxo-2,4,5,5a,5b,6,7,8,8a,8b-decahydro-1*H*-azeto[2,3-e]furo[2,3-g]isoindole-1-carboxylate (6e): Using *tert*-butyl 3-(4,5-dihydrofuran-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **6e** (0.44 mmol, 150 mg, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, J = 6.5, 4.4 Hz, 1H), 4.43 (t, J = 9.4 Hz, 2H), 3.86 (t, J = 7.3 Hz, 1H), 3.46 (d, J = 7.1 Hz, 1H), 3.30 – 3.25 (m, 1H), 3.24 – 3.20 (m, 1H), 2.90 (s, 3H), 2.88 – 2.80 (m, 2H), 2.74 – 2.71 (m 1H), 1.34 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 175.3, 158.1, 153.6, 100.1, 80.7, 77.2, 70.1, 61.0, 53.2, 44.0, 41.1, 32.4, 28.1, 27.4, 25.1.ppm. LRMS (DEP/EI-Orbitrap): m/z 234.2 (8), 205.1 (42), 177.1 (11). HRMS (EI-Orbitrap): calcd for $C_{17}H_{22}N_2O_5^+$: 334.1529; found: 334.1518. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2932 (w), 2898 (w), 2254 (vw), 1780 (w), 1696 cm^{-1} (vs). mp (°C): 170 – 174.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-3-ethoxy-6-methyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**6f**): Using *tert*-butyl 3-(1-ethoxyvinyl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **6f** (0.39 mmol, 130 mg, 77%) as white solid. Rf = 0.1 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 – 4.71 (m, 1H), 4.63 (dt, J = 11.2, 2.6 Hz, 1H), 4.42 – 4.37 (m, 1H), 3.72 (qd, J = 7.1, 4.1 Hz, 2H), 3.35 (s, 1H), 3.05 (t, J = 6.7 Hz, 1H), 2.95 (s, 3H), 2.62 (d, J = 15.5, 1H), 2.29 – 2.19 (m, 1H), 1.46 (s, 9H), 1.17 ppm (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 174.4, 156.0, 145.2, 95.6, 80.2, 64.6, 64.1, 55.1, 41.8, 40.9, 28.4, 27.5, 25.3, 14.8 ppm. LRMS (ESI-quadrupole pos): m/z (%): 337.2 (40), 281.1 (100), 253.0 (5), 237.1 (2). HRMS (ESI-quadrupole pos): calcd for $C_{17}H_{25}N_2O_5^+$: 337.1758, found 337.1761. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2982 (w), 2932 (w), 2874 (w), 2252 (vw), 2154 (vw), 1778 (w), 1696 (s), 1560 cm^{-1} (vw). mp (°C): 120 – 125.

***tert*-Butyl-(4*R**,4a*R**,7a*R**,7b*R**)-3,4-dimethyl-5,7-dioxo-6-phenyl-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**6g**): Using *tert*-butyl (*Z*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate and 1-phenyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **6g** (0.48 mmol, 190 mg, 96%) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.18 – 7.15 (m, 2H), 5.05 – 4.94 (m, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.26 (d, J = 11.4 Hz, 1H), 3.61 (t, J = 9.0 Hz, 1H), 3.08 (dd, J = 8.3, 1.6 Hz, 1H), 3.01 (q, J = 7.3 Hz, 1H), 1.67 (s, 3H), 1.48 (s, 9H), 1.13 (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 173.1, 157.3, 132.9, 132.1, 129.2, 128.6, 126.5, 123.9, 80.5, 77.2, 63.4, 56.3, 48.6, 42.5, 36.4, 28.4, 18.3, 17.7, 14.0 ppm. LRMS (DEP/EI-Orbitrap): m/z 282.1 (62), 265.1 (83), 248.1 (10), 237.2 (34), 221.2 (16), 207.1 (16), 194.1 (13), 172.2 (8). HRMS (EI-Orbitrap): calcd for $C_{22}H_{26}N_2O_4^+$: 382.1893; found: 382.1897. IR (Diamond-ATR,

neat) $\tilde{\nu}_{max}$: 2972 (w), 2932 (w), 2872 (w), 1780 (w), 1704 (vs), 1598 cm^{-1} (w). mp (°C): 145 – 149

***tert*-Butyl-(4a*R**,7a*S**,7b*S**)-3-ethoxy-6-methyl-5,7-dioxo-7b-(trimethylsilyl)-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**6h**): Using *tert*-butyl 3-(1-ethoxyvinyl)-4-(trimethylsilyl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **6h** (0.34 mmol, 140 mg, 67%) as white solid. Rf = 0.3 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (dd, J = 11.5, 2.7 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 3.74 (q, J = 7.0 Hz, 2H), 3.49 – 3.35 (m, 1H), 2.98 (t, J = 8.6 Hz, 1H), 2.95 (s, 3H), 2.49 (d, J = 16.5 Hz, 1H), 2.31 (dd, J = 16.1, 7.4 Hz, 1H), 1.47 (d, J = 17.9 Hz, 9H), 1.17 (t, J = 7.0 Hz, 3H), 0.18 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 176.5, 156.8, 145.2, 102.2, 81.9, 80.8, 65.9, 58.0, 56.7, 45.2, 42.8, 30.0, 26.8, 16.5, 0.0 ppm. LRMS (ESI-quadrupole pos): m/z (%): 363.4 (1), 351.4(50), 307.3 (100), 263.2 (20). HRMS (ESI-quadrupole pos): calcd for $C_{16}H_{23}N_2O_5Si^+$ [M–t-Bu]+: 351.1376; found: 351.1388. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2900 (vw), 2868 (vw), 1778 (w), 1700 cm^{-1} (vs). mp (°C): 130 – 132.

***tert*-Butyl-(4a*R**,7a*S**,7b*S**)-3,6-dimethyl-5,7-dioxo-7b-(trimethylsilyl)-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**6i**): Using *tert*-butyl 3-(prop-1-en-2-yl)-4-(trimethylsilyl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **6i** (0.37 mmol, 140 mg, 74%) as white solid. Rf = 0.3 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (d, J = 12.5 Hz, 1H), 4.23 (d, J = 12.3 Hz, 1H), 3.54 – 3.40 (m, 1H), 2.98 (t, J = 6.9 Hz, 1H), 2.94 (s, 3H), 2.46 (d, J = 15.9, 1H), 2.30 – 2.19 (m, 1H), 1.62 (s, 3H), 1.57 – 1.41 (m, 9H), 0.19 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 174.9, 128.9, 123.7, 80.7, 60.5, 44.4, 41.7, 29.4, 28.6, 25.4, 21.2, 18.6, 18.6, -1.4 ppm. LRMS (DEP/EI-Orbitrap): m/z 333.3 (2), 321.8 (15), 277.2 (100), 263.2 (30). HRMS (EI-Orbitrap): calcd for $C_{19}H_{30}N_2O_4Si^+$: 378.1975, found 378.1963 IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (w), 2948 (w), 2934 (w), 2902 (vw), 2864 (vw), 1778 (w), 1698 cm^{-1} (vs).

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-hydroxy(phenyl)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**12a**): Using *tert*-butyl 4-(hydroxy(phenyl)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **12a** (0.44 mmol, 180 mg, 62%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 5H), 6.32 (s, 1H), 4.56 (s, 1H), 4.14 (d, J = 8.4 Hz, 1H), 3.69 (d, J = 12.0 Hz, 1H), 3.15 (t, J = 7.4 Hz, 1H), 2.97 (d, J = 11.9 Hz, 1H), 2.83 (s, 3H), 2.53 (d, J = 15.3 Hz, 1H), 2.42 (dd, J = 15.5, 6.5 Hz, 1H), 1.43 (s, 3H), 1.35 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 175.3, 157.2, 140.0, 127.8, 127.7, 126.9, 126.8, 81.1, 79.4, 77.2, 74.8, 55.6, 43.4, 41.6, 29.4, 28.4, 25.5, 18.3 ppm. LRMS (DEP/EI-Orbitrap): m/z 294.1 (100), 279.1 (48), 222.2 (8), 208.2 (23). HRMS (EI-Orbitrap): calcd for $C_{23}H_{29}N_2O_5^+$: 413.2071; found: 413.2054. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3306 (vw), 2976 (w), 2932 (w), 2868 (vw), 1776 (w), 1698 (vs), 1662 cm^{-1} (s).

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-[1,1'-biphenyl]-4-yl(hydroxy)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**12b**): Using *tert*-butyl (*S**)-4-([1,1'-biphenyl]-4-yl(hydroxy)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **12b** (0.47 mmol, 227 mg, 93%) as white solid. Rf = 0.2 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.7 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.36 (dd, J = 7.7, 5.8 Hz, 3H), 6.51 (s, 1H), 4.75 (s, 1H), 4.32 (d, J = 8.4 Hz, 1H), 3.88 (d, J = 12.1 Hz, 1H), 3.32 (t, J = 7.7 Hz, 1H), 3.27 – 3.21 (m, 1H), 2.99 (s, 3H), 2.71 (dd, J = 15.7, 1.6 Hz, 1H), 2.60 (dd, J = 16.3, 7.1 Hz, 1H), 1.60 (s, 3H), 1.51 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 175.3, 157.3, 140.7, 140.4, 139.2, 129.0, 127.5, 127.3, 127.1, 127.1, 126.9, 126.5, 81.3, 79.5, 74.7, 55.7, 43.5, 41.7, 29.5, 28.5, 25.6, 18.4 ppm. LRMS (DEP/EI-Orbitrap): m/z 489.3 (2). 447.3 (2), 374.2 (10), 306.2 (20). HRMS (EI-Orbitrap): calcd for $C_{29}H_{33}N_2O_5^+$: 489.2384, found 489.2410 IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3300 (vw), 2978 (vw), 2932 (vw), 2868 (vw), 2252 (vw), 1776 (w), 1700 (s), 1660 (m), 1600 (vw), 1520 cm^{-1} (vw). mp (°C): 165 – 170.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-(4-cyanophenyl)(hydroxy)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**12c**): Using *tert*-butyl 4-((4-cyanophenyl)(hydroxy)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **12c** (0.4 mmol, 175 mg, 80%) as yellow solid. Rf = 0.1 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 6.62 (d, J = 10.4 Hz, 1H), 4.72 (d, J = 8.6 Hz, 1H), 4.24 (d, J = 8.4 Hz, 1H), 3.87 (d, J = 12.2 Hz, 1H), 3.30 (t, J = 7.7 Hz, 1H), 3.13 (d, J = 12.3 Hz, 1H), 2.95 (s, 3H), 2.69 (d, J = 15.7, 1H), 2.54 (dd, J = 15.9, 7.4 Hz, 1H), 1.58 (s, 3H), 1.46 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 174.9, 157.1, 145.8, 131.6, 128.3, 127.5, 126.2, 118.8, 111.6, 81.6, 79.1, 74.3, 55.5, 43.3, 41.4, 29.6, 28.4, 25.5, 18.4 ppm. LRMS (DEP/EI-Orbitrap): m/z 379.4 (2), 321.3 (5). HRMS (EI-Orbitrap): calcd for $C_{24}H_{28}N_3O_5^+$: 438.2023, found 438.2013 IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3286 (vw), 2980 (vw), 2254 (vw), 2230 (vw), 1776 (vw), 1700 (m), 1658 (w), 1610 cm^{-1} (vw). mp (°C): 160 – 165.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-hydroxy(4-nitrophenyl)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**12d**): Using *tert*-butyl (*S**)-4-(hydroxy(4-nitrophenyl)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **12d** (0.42 mmol, 190 mg, 83%) as yellow solid. R_f = 0.1 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.71 (s, 1H), 4.79 (s, 1H), 4.28 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 12.2 Hz, 1H), 3.33 (t, J = 7.2 Hz, 1H), 3.18 (d, J = 11.9 Hz, 1H), 2.99 (s, 3H), 2.73 (d, J = 15.7, 1H), 2.59 (dd, J = 15.3, 7.3 Hz, 1H), 1.61 (s, 3H), 1.50 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 174.9, 157.2, 147.9, 147.6, 128.5, 127.8, 126.2, 123.0, 81.9, 79.2, 74.3, 55.6, 43.3, 41.5, 29.7, 28.4, 25.6, 18.5 ppm. LRMS (ESI-quadrupole pos): m/z (%): 458.2 (100), 402.1 (20), 251.1 (10). HRMS (ESI-quadrupole pos): calcd for $C_{23}H_{28}N_3O_7^+$: 458.1922, found 458.1922. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3276 (vw), 2978 (w), 2934 (w), 2868 (vw), 1776 (w), 1698 (s), 1658 (m), 1606 (w), 1520 cm^{-1} (m). mp (°C): 152 – 155.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*R**)-furan-2-yl(hydroxy)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**12e**): Using *tert*-butyl 4-(furan-2-yl(hydroxy)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **12e** (0.35 mmol, 140 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.40 (d, J = 9.2 Hz, 1H), 6.35 (s, 1H), 6.28 (d, J = 3.1 Hz, 1H), 4.65 (d, J = 7.7 Hz, 1H), 4.20 (d, J = 8.5 Hz, 1H), 3.96 (d, J = 11.9 Hz, 1H),

3.61 (d, J = 11.9 Hz, 1H), 3.20 (t, J = 7.4 Hz, 1H), 2.96 (s, 3H), 2.61 (d, J = 15.6 Hz, 1H), 2.41 (dd, J = 15.5, 6.0 Hz, 1H), 1.58 (s, 3H), 1.47 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 175.0, 157.5, 153.6, 142.1, 127.3, 125.8, 110.5, 107.8, 81.2, 78.1, 77.2, 69.8, 55.7, 43.2, 41.6, 28.9, 28.4, 25.5, 18.5 ppm. LRMS (ESI-quadrupole pos): m/z (%): 284.1 (100), 269.1 (21), 241.2 (5), 210.0 (6), 198.1 (12), 184.1 (67), 170.1 (8). HRMS (ESI-quadrupole pos): calcd for $C_{21}H_{27}N_2O_6^+$: 403.1864; found: 403.1926. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3298 (vw), 2974 (w), 2930 (w), 2870 (w), 1778 (w), 1698 (vs), 1668 cm^{-1} (s). mp (°C): 157 – 160.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-hydroxy(1-methyl-1H-indol-3-yl)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**12f**): Using *tert*-butyl (*S**)-4-(hydroxy(1-methyl-1*H*-indol-3-yl)methyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **12f** (0.41 mmol, 191 mg, 82%) as brown oil. R_f = 0.1 (hexane/EtOAc 7:3, UV, KMnO4, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.3 Hz, 2H), 7.22 – 7.17 (m, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.29 (d, J = 11.0 Hz, 1H), 5.09 (d, J = 11.0 Hz, 1H), 4.40 (d, J = 8.5 Hz, 1H), 3.84 (d, J = 11.9 Hz, 1H), 3.79 (s, 3H), 3.36 – 3.26 (m, 2H), 3.00 (s, 3H), 2.78 – 2.65 (m, 2H), 1.52 ppm (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 175.5, 157.7, 136.9, 128.2, 127.0, 126.9, 126.9, 121.5, 119.2, 119.1, 114.6, 109.3, 80.7, 79.7, 69.7, 56.3, 43.6, 41.8, 33.0, 29.3, 28.5, 25.5, 18.4 ppm. LRMS (DEP/EI-Orbitrap): m/z 447.3 (2), 374.2 (10), 306.2 (20), 250.1 (100). HRMS (EI-Orbitrap): calcd for $C_{26}H_{31}N_3O_5^+$: 465.2264, found 465.2258. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3324 (vw), 2946 (vw), 2934 (vw), 2926 (vw), 2894 (vw), 2884 (vw), 2254 (vw), 1776 (vw), 1700 (m), 1662 (w), 1616 (vw), 1548 cm^{-1} (vw).

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-7b-((*S**)-1-hydroxy-2-methyl propyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1*H*-azeto[2,3-*e*]isoindole-1-carboxylate** (**12g**): Using *tert*-butyl 4-(1-hydroxy-2-methylpropyl)-3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate and 1-methyl-1*H*-pyrrole-2,5-dione according to general procedure **C**, provided **12g** (0.29 mmol, 110 mg, 58%) as a crystalline white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (s, 1H), 4.41 (d, J = 12.5 Hz, 1H), 4.26 – 4.12 (m, 2H), 3.28 (d, J = 4.1 Hz, 1H), 3.15 (t, J = 7.7 Hz, 1H), 2.94 (s, 3H), 2.48 (d, J = 15.5 Hz, 1H), 2.32 (d, J = 7.2 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.58 (s, 3H), 1.48 (s, 9H), 1.02 (d, J = 6.7 Hz, 3H), 0.98 ppm (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 175.6, 156.6, 127.8, 126.9, 81.1, 79.4, 77.2, 76.5, 55.6, 44.1, 41.5, 30.9, 30.0, 28.5, 25.4, 22.5, 18.4, 17.7 ppm. LRMS (DEP/EI-Orbitrap): m/z 305.2 (8), 250.2 (56), 217.2 (8), 205.2 (100). HRMS (EI-Orbitrap): calcd for $C_{20}H_{31}N_2O_5^+$: 379.2227; found: 379.2227. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3332 (vw), 2962 (w), 2934 (w), 2870 (w), 1776 (w), 1702 (vs), 1670 cm^{-1} (m). mp (°C): 134 – 138.

***tert*-Butyl-(4a*R**,7a*R**,7b*S**)-3,7a-dimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate-7b-d** (**14a**): Using *tert*-butyl 3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate-4-d and 3-methylfuran-2,5-dione according to general procedure **D**, provided **14a** (0.20 mmol, 62 mg, 40%) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (ddd, J = 12.3, 3.0, 1.8 Hz, 1H), 4.24 (d, J = 12.3 Hz, 1H), 2.97 (dd, J = 4.4, 2.7 Hz, 1H), 2.57 (dd, J = 15.2, 2.7 Hz, 1H), 2.20 (d, J = 14.1 Hz, 1H), 1.72 – 1.68 (s, 3H), 1.62 (s, 3H), 1.48 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 171.3, 157.1, 128.9, 125.8, 81.1, 77.2, 70.8, 56.1, 50.7, 49.8, 28.6, 28.3, 22.6, 18.5 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 196.2 (15), 140.1 (49). HRMS (EI-Orbitrap): calcd for $C_{16}H_{20}DNO_5^+$: 308.1482; found: 308.1479, found 322.1651 IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (w), 2935 (w), 2873 (vw), 1847 (w), 1779 (vs), 1697 cm^{-1} (s). mp (°C): 151 – 155.

***tert*-Butyl-(4a*R**,7a*R**,7b*R**)-3,4a-dimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate-7b-d** (**14b**): Using *tert*-butyl 3-(prop-1-en-2-yl)azete-1(2*H*)-carboxylate-4-d and 3-methylfuran-2,5-dione according to general procedure **D**, provided **14b** (0.7 mmol, 20 mg, 14%) as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (d, J = 12.4 Hz, 1H), 4.30 (d, J = 12.4 Hz, 1H), 3.31 (s, 1H), 2.51 (d, J = 15.0 Hz, 1H), 2.04 (d, J = 14.9 Hz, 1H), 1.68 (s, 3H), 1.48 (s, 9H), 1.46 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 167.3, 156.4, 128.4, 125.9, 80.8, 77.2, 63.2, 55.7, 50.5, 49.1, 37.9, 28.4, 24.2, 18.1 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 196.2 (15), 140.1 (49). HRMS (EI-Orbitrap): calcd for $C_{16}H_{20}DNO_5^+$: 308.1482; found: 308.1479. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2977 (w), 2935 (w), 2873 (vw), 1847 (w), 1779 (vs), 1697 cm^{-1} (s). mp (°C): 151 – 155.

***tert*-Butyl-(4*S**,4a*R**,7a*R**,7b*S**)-3,4,7a-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate** (**15a**): Using tert-butyl (*E*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate and 3-methylfuran-2,5-dione according to general procedure **D**, provided **15a** (0.18 mmol, 58 mg, 36%) as white solid. R_f = 0.5 (hexane/EtOAc 7:3, UV, KMnO4, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 – 4.42 (m, 1H), 4.32 (s, 1H), 4.25 (d, J = 12.5 Hz, 1H), 2.77 (d, J = 3.1 Hz, 1H), 2.48 – 2.36 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.52 (s, 3H), 1.49 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 171.0, 157.1, 133.0, 126.0, 81.2, 71.4, 57.2, 55.5, 51.0, 32.6, 28.4, 21.7, 14.3, 14.2 ppm. LRMS (ESI-quadrupole pos): m/z (%): 322.2 (85), 266.1 (100). HRMS (ESI-quadrupole pos): calcd for $C_{17}H_{24}NO_5^+$: 322.1649, found 322.1651 IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2998 (w), 2978 (w), 2946 (w), 2920 (w), 1846 (m), 1774 (s), 1676 cm^{-1} (vs). mp(°C): 169-173.

***tert*-Butyl-(4*R**,4a*R**,7a*R**,7b*R**)-3,4,4a-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate** (**15b**): Using *tert*-butyl (*E*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate and 3-methylfuran-2,5-dione according to general procedure **D**, provided **15b** (0.05 mmol, 14 mg, 9%) as white solid. Rf = 0.45 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, J = 7.1 Hz, 1H), 4.54 (d, J = 12.5, 1H), 4.35 (d, J = 12.5 Hz, 1H), 3.37 (s, 1H), 2.25 (d, J = 7.7 Hz, 1H), 1.63 (s, 3H), 1.48 (s, 12H), 1.36 ppm (d, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 167.7, 156.1, 131.4, 128.0, 80.7, 62.9, 56.0, 52.2, 39.8, 29.8, 28.5, 22.3, 14.0, 11.0 ppm. LRMS (ESI-quadrupole pos): m/z (%): 322.2 (85), 266.1 (100). HRMS (ESI-quadrupole pos): calcd for $C_{17}H_{24}NO_5^+$: 322.1649, found 322.1651 IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (m), 2936 (m), 2872 (m), 1854 (m), 1780 (vs), 1738 (m), 1698 (s), 1658 cm^{-1} (m).

***tert*-Butyl-(4*R**,4a*R**,7a*R**,7b*S**)-3,4,7a-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate-7b-d** (**16a**): Using *tert*-butyl (*Z*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate-4-d and 3-methylfuran-2,5-dione according to general procedure **D**, provided **16a** (0.25 mmol, 80 mg, 50%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, J = 12.1 Hz, 1H), 4.25 (d, J = 12.1 Hz, 1H), 2.97 (qd, J = 7.3, 2.1 Hz, 1H), 2.85 (d, J = 2.2 Hz, 1H), 1.69 (s, 6H), 1.50 (s, 9H), 1.12 ppm (d, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 171.3, 157.4, 134.0, 124.6, 81.2, 77.2, 70.1, 56.5, 50.0, 37.7, 31.1, 28.3, 24.8, 17.7, 17.3 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 222.0 (3), 210.2 (25). HRMS (EI-Orbitrap): calcd for $C_{17}H_{22}DNO_5^+$: 322.1639; found: 322.1630. IR (Diamond-ATR,

neat) $\tilde{\nu}_{max}$: 2972 (w), 2932 (w), 2874 (w), 1854 (w), 1780 (vs), 1706 cm^{-1} (s). mp (°C): 170 – 173.

***tert*-Butyl-(4*S**,4a*R**,7a*R**,7b*R**)-3,4,4a-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate-7b-d** (**16b**): Using *tert*-butyl (*Z*)-3-(but-2-en-2-yl)azete-1(2*H*)-carboxylate-4-d and 3-methylfuran-2,5-dione according to general procedure **D**, provided **16b** (0.06 mmol, 20 mg, 12%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, J = 12.4 Hz, 1H), 4.25 (d, J = 12.0 Hz, 1H), 3.27 (s, 1H), 2.62 (q, J = 7.3 Hz, 1H), 1.69 (s, 3H), 1.48 (s, 9H), 1.42 (s, 3H), 1.01 ppm (d, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 167.6, 157.3, 136.0, 123.5, 81.0, 77.2, 62.8, 53.6, 51.4, 40.8, 31.1, 28.5, 22.7, 17.7, 13.7 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 222.0 (3), 210.2 (25). HRMS (EI-Orbitrap): calcd for $C_{17}H_{22}DNO_5^+$: 322.1639; found: 322.1630. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2954 (m), 2924 (s), 2854 (m), 1852 (w), 1782 (vs), 1706 cm^{-1} (s). mp (°C): 170 – 173.

***tert*-Butyl-(4a*R**,7a*R**,7b*S**)-3,4,4,7a-tetramethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-*b*]azete-1(2*H*)-carboxylate** (**17a**)

Using *tert*-butyl 3-(3-methylbut-2-en-2-yl)azete-1(2*H*)-carboxylate and 3-methylfuran-2,5-dione according to general procedure **D**, provided **17a** (0.45 mmol, 150 mg, 89%) as a yellowish solid. Only one regioisomer was isolated (ratio greater than 10:1 in crude ^{13}C NMR): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 – 4.57 (m, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.20 (d, J = 11.8 Hz, 1H), 2.64 (s, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.49 (s, 9H), 1.08 ppm (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170.5, 157.6, 137.2, 125.5, 81.2, 77.2, 71.2, 61.8, 56.2, 51.1, 39.5, 28.5, 28.3, 27.6, 24.3, 14.2 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 235.1 (3), 223.2 (23), 167.1 (100). HRMS (EI-Orbitrap): calcd for $C_{18}H_{24}NO_5^+$ [M-H]$^+$: 334.1654; found: 334.1646. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2938 (w), 2874 (w), 1844 (w), 1780 (vs), 1702 cm^{-1} (vs). mp (°C): 121 – 125.

***tert*-Butyl-3-methoxy-3-phenylazetidine-1-carboxylate** (**18a**): Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and phenylmagnesium bromide according to general procedure **B**, provided 18a (7.80 mmol, 2.101 g, 98%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.26 (m, 5H), 4.17 (s, 4H), 3.08 (s, 3H), 1.45 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 140.0, 128.8, 128.2, 126.2, 79.9, 76.8, 59.2, 51.7, 28.5 ppm. LRMS (ESI-quadrupole pos): m/z (%): 190.1 (6), 175.1 (12). HRMS (ESI-quadrupole pos): calcd for $C_{15}H_{22}NO_3^+$: 264.1594; found: 264.1594. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2978 (w), 2950 (w), 2884 (w), 2828 (vw), 1702 cm^{-1} (vs).

***tert*-Butyl-3-methoxy-3-(4-methoxyphenyl)azetidine-1-carboxylate** (**18b**): Using *tert*-butyl 3-oxoazetidine-1-carboxylate (**1**) and (4-methoxyphenyl)magnesium bromide according to general procedure **B**, provided **18b** (3.75 mmol, 1.100 g, 75%) as colorless oil. Rf = 0.5 (hexane/EtOAc 9:1, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.11 (s, 4H), 3.77 (s, 3H), 3.00 (s, 3H), 1.41 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.5, 131.7, 127.5, 113.9, 79.6, 76.3, 60.4, 58.4, 55.2, 51.3, 28.3 ppm. LRMS (ESI-quadrupole pos): m/z (%): 294.2 (85), 279.1 (45). HRMS (ESI-quadrupole pos): calcd for $C_{16}H_{24}NO_4^+$: 294.1700, found 294.1702. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974 (w), 2938 (w), 2882 (w), 2836 (vw), 1698 (vs), 1612 cm^{-1} (m).

***tert*-Butyl-3-methoxy-3-(phenylethynyl)azetidine-1-carboxylate** (**18c**): Commercially available phenylacetylene (1.0 eq., 20 mmol) was dissolved in THF (60 mL) and cooled to -78 °C. After cooling, *n*-BuLi (1.0 eq., 2.44 M, 20 mmol) was added dropwise and the solution stirred for one hour before adding dropwise a solution of tert-butyl 3-oxoazetidine-1-carboxylate (**1**) (0.8 eq, 16 mmol, in 10 mL THF). The reaction mixture was quenched with saturated NH_4Cl and extracted twice with diethyl ether (2x 40 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated under vacuum. The crude alcohol was then redissolved in THF (60 mL) and cooled to 0 °C. After adding sodium hydride (1.0 eq., 20 mmol) portionwise, the reaction mixture was allowed to reach room temperature and stirred for one hour. Methyl iodide (1.0 eq., 20 mmol) was then added and the mixture stirred for two more hours at room temperature. The reaction was quenched with methanol and the solvents were evaporated. Purification by column chromatography on silica gel gave substituted 3-substituted 1-boc-3-methoxyazetidines **18c** (11.8 mmol, 3.398 g, 74%) as yellow solid. R_f = 0.80 (hexane/EtOAc 8:2, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.38 – 7.31 (m, 3H), 4.18 (d, J = 9.0 Hz, 2H), 4.08 (d, J = 9.0 Hz, 2H), 3.41 (s, 3H), 1.45 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 131.9, 129.0, 128.5, 122.0, 87.7, 86.2, 80.1, 68.4, 61.8, 52.8, 28.5 ppm. LRMS (ESI-quadrupole pos): m/z (%): 288.1 (30), 273.1 (85), 232.1 (100). HRMS (EI-Orbitrap): calcd for $C_{17}H_{22}NO_3^+$ [2M+H]$^+$: 288.1594, found 288.1595. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2996(vw), 2974(w), 2952(w), 2932(w), 2880(w), 2230(vw), 1692(s).

***tert*-Butyl-3-ethyl-3-methoxyazetidine-1-carboxylate** (**18d**): Using ethylmagnesium chloride according to general procedure **B** afforded **18d** (7.38 g, 69%). Colorless oil, R_f = 0.24 (10% EtOAc in hexane, PAA, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ: 3.84 (d, J = 9.0 Hz, 2H), 3.66 (d, J = 8.9 Hz, 2H), 3.20 (s, 3H), 1.78 (q, J = 7.3 Hz, 2H), 1.44 (s, 9H), 0.88 ppm (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ: 156.7, 79.7, 75.4, 58.0, 50.5, 28.5, 27.2, 7.1 ppm. LRMS (ESI-quadrupole pos) m/z (%): not found. HRMS (ESI-quadrupole pos): not found. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2938 (w), 2882 (w), 1740 (m), 1704 cm^{-1} (vs).

***tert*-Butyl-(4a*S**,7a*S**,7b*S**)-3,6-dimethyl-5,7-dioxo-7b-phenyl-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate** (**8a**): Using **18a** and 2-bromoprop-1-ene according to general procedure **E**, provided **8a** (0.46 mmol, 174 mg, 91%) as a yellowish oil. R_f = 0.6 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 4.3 Hz, 4H), 7.33 – 7.27 (m, 1H), 4.82 (d, J = 7.9 Hz, 1H), 3.64 (d, J = 7.9 Hz, 1H), 3.50 (d, J = 8.5 Hz, 1H), 3.05 (s, 3H), 2.96 (t, J = 7.3 Hz, 1H), 2.40 (d, J = 15.1 Hz, 1H), 2.23 (dd, J = 15.3, 6.4 Hz, 1H), 2.02 (s, 3H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 177.4, 151.6, 142.2, 137.4, 129.5, 127.5, 126.1, 106.8, 81.0, 61.3, 47.4, 46.9, 42.3, 29.1, 28.4, 25.6, 18.0 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 382.3 (20), 326.2 (90), 281.2 (100). HRMS (EI-Orbitrap): calcd for $C_{22}H_{26}N_2O_4^+$ [M]+: 382.1893 found 382.1890. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (vw), 2930 (vw), 2858 (vw), 1774 (w), 1730 (w), 1700 cm^{-1} (vs).

***tert*-Butyl-(4*R**,4a*S**,7a*S**,7b*S**)-3,4,6-trimethyl-5,7-dioxo-7b-phenyl-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate** (**8b**): Using **18a** and (*E*)-2-bromobut-2-ene according to general procedure E, provided **8b** (0.31 mmol, 123 mg, 62%) as a yellowish oil. R_f = 0.6 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 4H), 7.33 – 7.27 (m, 1H), 4.72 (d, J = 8.0 Hz, 1H), 3.58 (dd, J = 8.1, 5.8 Hz, 2H), 3.01 (s, 3H), 2.90 (dd, J = 8.2, 5.0 Hz, 1H), 2.49 (p, J = 7.0 Hz, 1H), 1.99 (s, 3H), 1.43 (s, 9H), 1.36 ppm (d, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 177.2, 151.6, 142.1, 138.1, 129.5, 127.5, 125.8, 111.1, 80.9, 61.5, 48.6, 48.3, 47.4, 31.8, 28.4, 25.2, 14.3, 12.8 ppm. LRMS (DEP/EI-Orbitrap):

m/z (%): 355.0 (5), 295.1 (100), 265.1 (20), 182.1 (85). HRMS (EI-Orbitrap): calcd for $C_{23}H_{28}N_2O_4^+$ [M]+: 396.2049 found 396.2040. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976(w), 2906(vw), 1770(w), 1692 cm^{-1} (vs).

***tert*-Butyl-(4*S**,4a*S**,7a*S**,7b*S**)-4-(4-chlorobutyl)-6-methyl-5,7-dioxo-7b-phenyl-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate** (**8c**): Using **18a** and (*E*)-6-chloro-1-iodohex-1-ene according to general procedure **E**, provided **8c** (0.33 mmol, 149 mg, 65%) as a yellowish oil. R_f = 0.5 (hexane/EtOAc 7:3, UV, KMnO4, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 4H), 7.34 – 7.28 (m, 1H), 5.25 (s, 1H), 4.88 (s, 1H), 3.69 (d, J = 7.8 Hz, 1H), 3.60 (d, J = 8.1 Hz, 1H), 3.52 (t, J = 6.6 Hz, 2H), 3.02 – 2.97 (m, 4H), 2.30 (dtd, J = 9.9, 6.0, 3.9 Hz, 1H), 1.88 – 1.70 (m, 4H), 1.57 – 1.47 (m, 2H), 1.44 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 152.2, 145.0, 141.2, 134.3, 129.6, 127.7, 125.9, 100.1, 81.5, 47.8, 46.9, 46.2, 45.1, 34.5, 32.6, 31.2, 28.3, 25.6, 25.2 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 458.4 (10), 402.2 (60), 357.3 (25), 323.3 (65), 291.2 (70), 267.2 (100), 247.2 (50), 194.1 (5). HRMS (EI-Orbitrap): calcd for $C_{25}H_{31}ClN_2O_4^+$ [M]+: 458.1972 found 458.1969. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2936 (w), 2866 (vw), 1770 (w), 1694 cm^{-1} (vs).

***tert*-Butyl-(4*R**,4a*S**,7a*S**,7b*S**)-7b-(4-methoxyphenyl)-3,4,6-trimethyl-5,7-dioxo-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate** (**8d**): Using **18b** and (*E*)-2-bromobut-2-ene according to general procedure **E**, provided **8d** (0.32 mmol, 156 mg, 64%) as a yellowish oil. R_f = 0.45 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.69 (d, J = 8.0 Hz, 0H), 3.79 (s, 1H), 3.53 (t, J = 8.6 Hz, 1H), 2.98 (s, 1H), 2.87 (dd, J = 8.1, 5.0 Hz, 1H), 2.48 (p, J = 7.0 Hz, 1H), 1.96 (s, 1H), 1.42 (s, 4H), 1.34 ppm (d, J = 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 176.9, 159.0, 152.2, 145.3, 133.0, 127.0, 114.8, 99.9, 81.4, 55.4, 47.8, 46.1, 45.1, 34.4, 32.6, 31.1, 28.3, 25.6, 25.2 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 426.3 (5), 370.3 (100), 325.3 (90), 311.2 (80). HRMS (EI-Orbitrap): calcd for $C_{24}H_{30}N_2O_5^+$ $[M]^+$: 426.2155 found 426.2155. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976 (w), 2936 (vw), 1770 (w), 1698 (vs), 1610 cm^{-1} (vw).

***tert*-Butyl-(4*S**,4a*S**,7a*S**,7b*S**)-4-(4-chlorobutyl)-7b-(4-methoxyphenyl)-6-methyl-5,7-dioxo-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate** (**8e**)
Using **18b** and (*E*)-6-chloro-1-iodohex-1-ene according to general procedure **E**, provided **8e** (0.32 mmol, 156 mg, 64%) as a yellowish oil. R_f = 0.4 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 5.21 (s, 1H), 4.85 (s, 1H), 3.79 (s, 3H), 3.64 (d, J = 7.7 Hz, 1H), 3.55 (d, J = 8.2 Hz, 1H), 3.51 (t, J = 6.6 Hz, 2H), 3.04 – 2.92 (m, 4H), 2.34 – 2.24 (m, 1H), 1.77 (dqq, J = 19.3, 12.5, 6.0, 5.4 Hz, 4H), 1.57 – 1.45 (m, 2H), 1.43 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 177.2, 158.9, 151.6, 138.4, 133.9, 126.9, 114.7, 110.8, 80.8, 61.7, 60.5, 55.4, 48.6, 47.6, 47.4, 31.6, 28.3, 25.1, 21.1, 14.3, 12.8 ppm. LRMS (DEP/EI-Orbitrap): m/z (%): 488.4 (2), 459.2 (2), 432.3 (100), 387.3 (80), 377.3 (50). HRMS (EI-Orbitrap): calcd for $C_{26}H_{33}ClN_2O_5^+$ $[M]^+$: 488.2078 found 488.2059. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2972 (w), 2954 (w), 2936 (w), 1770 (w), 1696 cm^{-1} (vs).

***tert*-Butyl-(4a*S**,7a*S**,7b*R**)-7b-ethyl-3,6-dimethyl-5,7-dioxo-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate** (**8f**): Using **18d** and 2-bromoprop-1-ene according to general procedure **E**, provided **8f** (0.43 mmol, 144 mg, 86%) as a yellowish oil. Yellow oil, R_f = 0.29 (20% EtOAc in hexane, UV, PAA, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ: 4.27 (d, J = 8.4 Hz, 1H), 3.65 (d, J = 8.4 Hz, 1H), 3.12 – 3.04 (m, 1H), 3.00 (s, 3H), 2.94 (d, J = 8.6 Hz, 1H), 2.44 (d, J = 2.6 Hz, 2H), 1.87 (s, 3H), 1.74 – 1.64 (m, 2H), 1.45 (s, 9H), 1.00 ppm (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ: 179.8, 177.7, 151.7, 138.4, 105.3, 80.8, 56.1, 44.1, 44.0, 42.3, 28.7, 28.5, 28.3, 25.5, 18.0, 8.4 ppm. LRMS (ESI-quadrupole pos) m/z (%): 335.2 (95), 279.1 (100). HRMS (ESI-quadrupole pos): calcd for $C_{18}H_{27}N_2O_4^+$: 335.1965, found 335.1968.

***tert*-Butyl-(4a*S**,7a*S**,7b*S**)-3,6-dimethyl-5,7-dioxo-7*b*-(phenylethynyl)-1,4,4a,5,6,7,7a,7b-octahydro-2*H*-azeto[3,2-*e*]isoindole-2-carboxylate** (**8g**): Using **18c** and 2-bromoprop-1-ene according to general procedure **E**, provided **8g** (0.34 mmol, 136 mg, 67%) as a yellowish oil. R_f = 0.5 (hexane/EtOAc 7:3, UV, $KMnO_4$, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.36 – 7.28 (m, 3H), 4.84 (d, J = 8.0 Hz, 1H), 4.11 (d, J = 8.0 Hz, 1H), 3.39 (d, J = 8.5 Hz, 1H), 3.23 (ddd, J = 8.3, 6.3, 1.7 Hz, 1H), 3.01 (s, 3H), 2.87 – 2.77 (m, 1H), 2.51 (dd, J = 15.0, 1.7 Hz, 1H), 1.92 (s, 3H), 1.47 ppm (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 175.8, 151.2, 135.7, 131.9, 128.7, 128.5, 122.4, 105.8, 88.5, 82.8, 81.4, 58.6, 46.3, 41.6, 36.8, 29.0, 28.4, 25.6, 17.8 ppm. HRMS (EI-Orbitrap): calcd for $C_{24}H_{26}N_2O_4^+$ $[M]^+$: 406.1893 found 406.1895. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976(w), 2960(w), 2932 (w), 2874 (vw), 1790 (w), 1776 (w), 1756 (w), 1698 cm^{-1} (vs).

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds and X-ray crystallographic data of compound **12g** can be found in the Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

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[16] CCDC 1548836 (**12g**) contains the supplementary crystallographic data for this paper