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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 2H-azetine synthesis, a regiodivergent approach to fused 2-, and 3-alkylideneazetides was designed via the intermediate formation of unprecedented vinylazetine structures. Concise sequences to the latter are described, from which expected unsaturated fused ring systems 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 as their incorporation in drugs has been leading a number of synthetic studies. 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).

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. While smaller and larger N-containing heterocycles have been intensively studied, the general formation of azetidines and alkylideneazetidines 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 through the key formation of an azetinyllithium intermediate 2 (Scheme 1). 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, 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. Employing either vinylmetal species (eq. 1) or performing the subsequent cross-coupling with vinyl halides (eq. 2) respectively furnishes 3- and 2-vinylazetines (Scheme 1). Upon addition of a dieneophile, a stereoselective [4+2]-cycladdition takes place, leading to fused alkylideneazetidines (AAz) and . The regiodivergence of the strategy simply comes from the nature of the embedded diene initially employed (3-vinylazetine or 4-vinylazetine).

Results and Discussion

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

Scheme 2. Preparation of 3-vinylazetidine building blocks.

Starting from these vinylazetidines , α-lithiation in the presence of s-BuLi promotes a β-elimination and an excess amount of s-BuLi yields the key azetinylithium intermediate that can then be trapped by the appropriate electrophile (H2O or TMSiCl, Scheme 3). Resulting dienes were subsequently engaged in a [4+2]-cycladdition with electron deficient dieneophiles 5 to afford fused AAz with excellent control over the stereochemical outcome of the transformation in all cases (dr = 97:3). While isopropenylmetal species (R1 = Me) led to 6a and 6b with good yields employing respectively maleic anhydride and 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 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 TMSiCl in the formation of 4 led to quaternary stereocenter containing AAz 6h and 6i in good yields and stereoselectivities.

Scheme 3. Three-step sequence towards fused AAz.

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 (Scheme 4) – obtained by intermediate addition of an aldehyde – could lead to a diasterecontrolled [4+2]-cycladdition. Benzaldehyde was first used on 4-azetinylithium species, furnishing the corresponding azetine carbinol (from N-phenylmaleimide) containing four consecutive stereocenters was 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 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 TMSiCl in the formation of 4 led to quaternary stereocenter containing AAz 6h and 6i in good yields and stereoselectivities.10-14

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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).

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.\(^*\)

In order to introduce a quaternary stereocenter \(\alpha\) to a carbonyl position, we next employed citraconic anhydride 13 as dienophile. Dienes 4g-i and 4l obtained after quenching with either \(\text{H}_2\text{O}\) or \(\text{D}_2\text{O}\) 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.\(^*\)

\(^*\) 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.\(^*\)

\(^*\) Indicated yields are calculated from compound 9 after the three-step sequence, including the extraction step, see supporting information.
**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 alkylidenazetidines 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$_2$Cl$_2$ was predried over CaCl$_2$ and distilled from CaH$_2$. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen, and the organomagnesium reagents stored under nitrogen.

**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 complete 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-oxoazetidin-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 vinyl lithium 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$_4$Cl and extracted twice with diethyl...
phases were combined and dried over Na₂SO₄ 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 (H₂O, TMSCl, D₂O, aldehydes), stirred for 30 minutes and warmed up to room temperature. After workup with saturated NH₄Cl and extraction with diethyl ether (2x 10 mL), the organic phases were combined and dried over Na₂SO₄. 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 (H₂O or D₂O), stirred for 30 minutes and warmed up to room temperature. After workup with saturated NH₄Cl and extraction with diethyl ether (2x 10 mL), the organic phases were combined and dried over Na₂SO₄. 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 Bi(Ot-Pr)₃, stirred for 60 minutes at 0 °C. After this time, Pd(dppf)Cl₂·DCM (4 mol%) as well as the corresponding vinyl-halo-genide (X = I or Br) was added and let stir for 24 h. After workup with saturated NH₄Cl and extraction with diethyl ether (2x 10 mL), the organic phases were combined and dried over Na₂SO₄. 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**

terr-Butyl-3-methoxy-3-(prop-1-en-2-yl)azetidine-1-carboxylate (9a): Using tert-butyl 3-oxoazetidin-1-carboxylate (1) and isopropanimagnesium bromide according to general procedure B, provided 9a (4.40 mmol, 1.00 g, 88%) as colorless oil. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 C₇H₁₄NO₂+: 212.1287; found: 212.1301. IR (Diamond-ATR, neat) ν̃_max: 2976 (w), 2946 (w), 2884 (w), 2826 (w), 1704 cm⁻¹ (vs).

terr-Butyl-(Z)-3-(but-2-en-2-yl)-3-methoxyazetidine-1-carboxylate (9b): Using tert-butyl 3-oxoazetidin-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. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) 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 (16), 153.1 (4), 112.1 (68). HRMS (ESI-quadrupole pos): calcd for C₇H₁₄NO₂⁺ [M-Br⁺]: 184.0974; found: 184.0984. IR (Diamond-ATR, neat) ν̃_max: 2978 (w), 2944 (w), 2884 (w), 2824 (w), 1694 cm⁻¹ (vs).

terr-Butyl-3-methoxy-3-(3-methylbut-2-en-2-yl)azetidine-1-carboxylate (9c): Using tert-butyl 3-oxoazetidin-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. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (101 MHz, CDCl₃) δ 156.7, 133.1, 124.1, 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 C₇H₁₄NO₂⁺ [M-Br⁺]: 198.1130; found: 198.1123. IR (Diamond-ATR, neat) ν̃_max: 2978 (w), 2942 (w), 2880 (w), 2822 (w), 2244 (w), 1704 cm⁻¹ (vs).

terr-Butyl-(E)-3-(but-2-en-2-yl)-3-methoxyazetidine-1-carboxylate (9d): Using tert-butyl 3-oxoazetidin-1-carboxylate (1) and vinyllithium according to general procedure B, provided 9d after purification on silica gel (hexane/ethyl acetate 9:1), (2.0 mmol, 482 mg, 50%) as colorless oil. Rf = 0.5 (hex-ether). IR (Diamond-ATR, neat) ν̃: 2978 (m), 2884 (w), 2836 (vw), 1702 cm⁻¹ (vs).
**tert-Butyl 3-(1-ethoxyvinyl)-3-methoxyazetidine-1-carboxylate (6f):** Using tert-butyl 3-(1-ethoxyvinyl)azetidin-1-carboxylate and 1-methyl-1H-pyrrole-2,5-dione according to general procedure C, provided 6f (0.48 mmol, 190 mg, 96%) as a yellow sticky foam. 1H NMR (400 MHz, CDCl₃) δ 8.49 (dt, 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). 13C NMR (100 MHz, CDCl₃) δ 177.4, 173.6, 157.3, 135.4, 129.2, 77.1, 66.3, 53.3, 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 C₂₃H₂₃NO₃: 334.1893; found: 334.1895. IR (Diamond-ATR, neat) νₑₚₒₓₑₚ: 2978 (w), 2934 (w), 2872 (w), 2254 (vw), 1778 (w), 1696 cm⁻¹ (s).

**tert-Butyl-(4aR,7aR,7bR)-3-methyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1H-azeto[2,3-e]pyrrole-2,5-dione (6e):** Using tert-butyl 3-(4,5-dihydrofurao-2-yl)azete-1(2H)-carboxylate and 1-methyl-1H-pyrrole-2,5-dione according to general procedure C, provided 6e (0.44 mmol, 150 mg, 88%) as a white solid. 1H NMR (400 MHz, CDCl₃) 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), 3.29 – 3.20 (m, 1H), 2.90 – 2.80 (m, 2H), 2.74 – 2.71 (m, 1H), 1.34 ppm (s, 3H). 13C NMR (100 MHz, CDCl₃) δ 176.6, 175.3, 153.6, 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 C₁₉H₂₁NO₃: 334.1528; found: 334.1518. IR (Diamond-ATR, neat) νₑₚₒₓₑₚ: 2976 (w), 2932 (w), 2898 (w), 2254 (vw), 1780 (w), 1696 cm⁻¹ (s).
neat) $\nu_{max}$: 2972 (w), 2932 (w), 2872 (w), 1780 (w), 1704 (vs), 1598 cm$^{-1}$ (w). mp (°C): 145 – 149

terr-Butyl-(4R*,7aS*,7bS*)-3-ethoxy-6-methyl-5,7-dioxo-7b-(trimethylsilyl)-2,4,4a,5,6,7,7a,7b-octahydropyrrole-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), 3.39 – 3.35 (m, 1H), 2.64 (d, J = 7.5 Hz, 1H), 2.11 (s, 3H), 1.98 (d, J = 16.5 Hz, 1H), 2.06 (s, 3H), 1.86 ppm (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 180.5, 175.3, 165.8, 154.6, 142.2, 133.1, 122.8, 73.6, 71.9, 69.3, 69.2, 56.0, 43.2, 42.8, 30.0, 26.8, 16.5, 0.0 ppm. LRMS (ESI-quadrupole pos): m/z 364.1 (4), 351.4 (50), 307.3 (100), 263.2 (20). HRMS (ESI-quadrupole pos): calculated for C$_{16}$H$_{24}$N$_{2}$O$_{3}$Si $[M+Na]^+$: 315.1376; found: 315.1388. IR (Diamond-ATR, neat) $\nu_{max}$: 2978 (w), 2900 (vw), 2868 (vw), 1778 (w), 1700 cm$^{-1}$ (vs). mp (°C): 130 – 132.

terr-Butyl-(4R*,7aS*,7bS*)-3,6-dimethyl-5,7-dioxo-7b-(trimethylsilyl)-2,4,4a,5,6,7,7a,7b-octahydropyrrole-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, 2H), 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, 16.8, 1.4 ppm. LRMS (DEP/El-orbitrap): m/z 333.3 (2), 321.3 (15), 277.2 (100), 263.2 (30). HRMS (El-orbitrap): calculated for C$_{10}$H$_{16}$N$_{2}$O$_{3}$Si: 378.1975, found 378.1963 IR (Diamond-ATR, neat) $\nu_{max}$: 2974 (w), 2948 (w), 2934 (w), 2902 (w), 2864 (vw), 1778 (w), 1698 cm$^{-1}$ (vs).

terr-Butyl-(4R*,7aR*,7bR*)-7b-((S*)-hydroxy(phenyl)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1H-azeto[2,3-ε]isoeindole-1-carboxylate (12a): Using terr-butyl 4-(hydroxy(phenyl)methyl)-3-(prop-1-en-2-yl)-azeto[2,3-ε]isoeindole-1-carboxylic acid and 1-methyl-1H-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 (d, 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, 127.6, 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/El-orbitrap): m/z 294.1 (100), 279.1 (48), 222.2 (8), 208.2 (23). HRMS (El-orbitrap): calculated for C$_{16}$H$_{24}$N$_{2}$O$_{3}$: 413.2071; found: 413.2054. IR (Diamond-ATR, neat) $\nu_{max}$: 3306 (vw), 2976 (w), 2932 (w), 2868 (vw), 1776 (w), 1698 (vs), 1662 cm$^{-1}$ (s).

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**tetr-Butyl-(4aR*,7aR*,7bR*)-7b-((5S)-hydroxy-1-methyl-1H-indol-3-yl)methyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1H-azeto[2,3-e]isoniode-1-carboxylate (12f):** Using tert-butyl (5S)-4-hydroxy-1-methyl-1H-indol-3-yl)methyl)-3-(prop-1-en-2-yl)azete-1(2H)-carboxylic acid and 1-methyl-1H-pyrrole-2,5-dione according to general procedure C, provided 12f (0.41 mmol, 191 mg, 82%) as colorless oil. 1H NMR (400 MHz, CDCl3) 8 7.30 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 5.09 (d, J = 11.0 Hz, 1H), 4.40 (d, J = 8.5 Hz, 1H), 3.84 (d, J = 11.0 Hz, 1H), 3.78 (s, 3H), 3.36 – 3.26 (m, 2H), 3.00 (s, 3H), 2.78 – 2.65 (m, 2H), 1.52 ppm (s, 12H).

**C NMR (101 MHz, CDCl3) 8 174.3, 167.7, 156.1, 131.4, 126.0, 121.6, 119.1, 114.1, 106.4, 99.3, 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 474.7 (2), 374.2 (10), 306.2 (20), 250.1 (100). HRMS (EI/Orbitrap, calcd for C20H18N2O6: 465.2264, found 465.2258. IR (Diamond-ATR, neat) 8max: 3324 (v), 2946 (v), 2934 (v), 2926 (v), 2894 (v), 2884 (v), 2254 (v), 1776 (v), 1700 (m), 1662 (w), 1616 (w), 1548 cm–1 (v).**

**tetr-Butyl-(4aR*,7aR*,7bR*)-7b-((5S)-1-hydroxy-2-methyl propyl)-3,6-dimethyl-5,7-dioxo-2,4,4a,5,6,7,7a,7b-octahydro-1H-azeto[2,3-e]isoniode-1-carboxylate (12g):** Using tert-butyl (1-hydroxy-2-methylpropyl)3- (prop-1-en-2-yl)azete-1(2H)carboxylic acid and 1-methyl-1H-pyrrole-2,5-dione according to general procedure C, provided 12g (0.29 mmol, 110 mg, 58%) as a crystalline white solid. 1H NMR (400 MHz, CDCl3) 8 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 = 6.7 Hz, 3H). 13C NMR (101 MHz, CDCl3) 8 179.5, 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): calculated for C14H14N2O6: 379.2227; found: 379.2227. IR (Diamond-ATR, neat) 8max: 3332 (v), 2962 (w), 2934 (w), 2870 (s), 1776 (w), 1702 (vs), 1670 (m) (mp): 134 – 138.

**tetr-Butyl-(4aR*,7aR*,7bS*)-3,7a-dimethyl-5,7-dioxo-4,4a,5,6,7,7a,7b-hexahydroisobenzofuro[4,5-b]azete-1(2H)-carboxylic acid (14a):** Using tert-butyl (Z)-3-(prop-1-en-2 yl)azete-1(2H)-carboxylic acid and 3-methylfuran-2,5-dione according to general procedure D, provided 14a (0.20 mmol, 62 mg, 40%) as colorless crystals. 1H NMR (400 MHz, CDCl3) 8 4.91 (d, J = 12.3 Hz, 1H), 4.05 (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, 3H), 1.48 ppm (s, 9H). 13C NMR (101 MHz, CDCl3) 8 172.6, 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): calculated for C10H14NO5: 308.1482; found: 308.1479, 308.1497, 2935 (w), 2873 (vw), 1847 (w), 1779 (vs), 1697 cm–1 (m) (mp): 151 – 155.

**tetr-Butyl-(4aR*,7aR*,7bR*)-3,4a-dimethyl-5,7-dioxo-4,4a,5,6,7,7a,7b-hexahydroisobenzofuro[4,5-b]azete-1(2H)-carboxylic acid (14b):** Using tert-butyl 3-(prop-1-en-2-yl)azete-1(2H)-carboxylic acid and 3-methylfuran-2,5-dione according to general procedure D, provided 14b (0.7 mmol, 20 mg, 14%) as colorless crystals. 1H NMR (400 MHz, CDCl3) 8 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). 13C NMR (101 MHz, CDCl3) 8 176.8, 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): calculated for C10H14NO5: 308.1482; found: 308.1479, 308.1497, 2977 (w), 2935 (w), 2873 (vw), 1847 (w), 1779 (vs), 1697 cm–1 (m) (mp): 151 – 155.
tert-Butyl-(4S*,4aR*,7aR*,7bR*)-3,4,4-trimethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-e]azete-1(2H)-carboxylate (1d): Using tert-butyl (Z)-3-(but-2-en-2-yl)azete-1(2H)-carboxylate-4 and 3-methylfuran-2,5-dione according to general procedure B, provided 1b (0.06 mmol, 20 mg, 12%) as white solid. \( ^1H \) 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, 3H), 1.42 (s, 3H), 1.01 ppm (d, J = 7.3 Hz, 3H). \(^1^C\) NMR (101 MHz, CDCl\(_3\) ) δ 176.8, 167.6, 157.3, 123.5, 81.0, 77.2, 62.8, 53.6, 51.4, 40.8, 31.1, 28.5, 22.7, 17.7, 13.3 ppm. LRMS (DEP/El-Orbitrap): m/z (%): 222.0 (3), 210.2 (25). HRMS (El-Orbitrap): calcd for C\(_{17}\)H\(_{20}\)NO\(_6\): 334.1654; found: 334.1646. IR (Diamond-ATR, neat) \( \nu_{\text{max}} \) = 3349 (w), 2974 (w), 2938 (w), 2878 (w), 2827 (w), 2793 (w), 2711 (w), 1731 (w), 1487 (s), 1393 (s), 1373 (s), 1359 (s), 1333 (s), 1281 (w), 1262 (s), 1139 (s), 1123 (s), 1035 (s), 980 (s), 939 (s), 846 (s), 690 (s), 625 (s), 469 (s), 431 (s). HRMS (E-Si-quadropole): m/z (%): 334.165 (100), 273.1 (85), 232.1 (100). IR (Diamond-ATR, neat) \( \nu_{\text{max}} \) = 2975 (wv), 2957 (wv), 2925 (wv), 2880 (wv), 2230 (v), 1692 (s).

tert-Butyl-3-ethyl-3-methoxyazetidine-1-carboxylate (1d): Using ethylmagnesium chloride according to general procedure B afforded 18d (7.38 g, 69%). Colorless oil. \( R_\text{f} \) = 0.24 (10% EtOAc in hexane, PAA). \(^1H\) 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 ppm (J = 7.3 Hz, 2H), 1.44 (s, 9H), 0.88 ppm (t, J = 7.3 Hz, 3H). \(^1^C\) NMR (101 MHz, CDCl\(_3\) ) δ: 156.7, 140.0, 131.9, 129.0, 128.5, 122.0, 87.7, 80.1, 68.4, 51.2, 28.5 ppm. LRMS (E-Si-quadropole): m/z (%): 382.3 (100). IR (Diamond-ATR, neat) \( \nu_{\text{max}} \) = 2978 (wv), 2958 (wv), 2882 (wv), 2827 (wv), 2795 (wv), 2718 (wv), 1734 (wv), 1692 (s).

tert-Butyl-(4S*,7aS*,7bS*)-3,4,4,7a-tetramethyl-5,7-dioxo-4,4a,5,7,7a,7b-hexahydroisobenzofuro[4,5-e]azete-1(2H)-carboxylate (1d): Using tert-butyl 3-methylfuran-2,5-dione according to general procedure B, provided 17a (0.45 mmol, 150 mg, 89%) as a yellowish solid. Only one regioisomer was isolated (ratio greater than 10:1 in crude \[^1\text{C}\) NMR: \(^1H\) 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). \(^1^C\) NMR (101 MHz, CDCl\(_3\) ) δ: 171.1, 170.5, 157.6, 137.2, 125.5, 81.1, 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/El-Orbitrap): m/z (%): 235.1 (3), 222.3 (23), 167.1 (100). HRMS (El-Orbitrap): calcd for C\(_{17}\)H\(_{20}\)NO\(_6\): M\(^+\) 334.1654; found: 334.1646. IR (Diamond-ATR, neat) \( \nu_{\text{max}} \) = 2976 (w), 2938 (w), 2874 (w), 1844 (w), 1780 (v), 1702 cm\(^{-1}\) (vs).
**tert-Butyl-(4S*,4aS*,7aS*,7bS*)-7b-(4-(4-chlorobuty1)-6-methyl-5,7-dioxo-7b-phenyl-1,4,4a,5,6,7,7a,7b-octahydro-2H-azeto[3,2-e]isooindole-2-carboxylate (8c): Using 18a and (E)-6-chloro-1-iodoex-1-one according to general procedure E, provided 8c (0.33 mmol, 149 mg, 65%) as a yellowish oil. Rf = 0.5 (hexane/EtOAc 7:3, UV, KMnO4, PAA). 1H NMR (400 MHz, CDCl3) δ 7.45 – 7.37 (m, 4H), 3.74 – 3.28 (m, 1H), 5.25 (s, 1H), 4.88 (s, 1H), 3.69 (d, J = 8.7 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 (td, 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). 13C NMR (101 MHz, CDCl3) 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 C23H13ClNO4+ [M]+: 458.1972 found 458.1969. IR (Diamond-ATR, neat) νmax: 2976 (w), 2936 (w), 2866 (vw), 1770 (w), 1694 cm−1 (vs).

**ASSOCIATED CONTENT**

**Supporting Information**

1H and 13C 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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**REFERENCES**


[14] Diastereoisomeric ratios were determined by 1H NMR and GC and the relative configuration was determined by X-ray measurements.


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