EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300889

RCM Approach to Complex Polycyclic α-Hydroxy γ-Lactams: Synthesis of Indolizinones and Pyrroloazepinones

Asier Gómez-SanJuan,[a] Nuria Sotomayor,[a] and Esther Lete*[a]

Keywords: Nitrogen heterocycles / Lactams / Ring-closing metathesis / Diastereoselectivity / Grignard reaction / α-Amidoalkylation

The allylmagnesium chloride addition/RCM sequence on *N*-alkenyl-substituted imides provides a mild access to indolizinone and pyrroloazepinone derivatives with the α-hydroxy-γ-lactam framework. The procedure can be applied to the asymmetric synthesis of this type of derivatives, by employing a 2-*exo*-hydroxy-10-bornylsulfinyl group as a chiral auxiliary. Further functionality can be introduced at the angular position through an α-amidoalkylation reaction.

Introduction

α-Hydroxy-γ-lactams and their derivatives are versatile building blocks that have been used to prepare numerous heterocyclic compounds, including alkaloids,[1] vitamins [e.g. (+)-biotin],[2] Carbacephem antibiotics,[3] angiotensin converting enzyme inhibitors,[4] and anthelmintic and anticancer drugs such as praziquantel[5] and (*R*)-(+)-Crispine A.[6]

Hydroxylactams are readily converted into the corresponding lactams,[7] and are precursors to *N*-acyliminium ions.[8] The α-amidoalkylation of π-nucleophiles using *N*-acyliminium ions as electrophiles is one of the most attractive methods for C–C bond formation in heterocyclic chemistry and has found widespread application in natural products synthesis.[8] Thus, our group has demonstrated the synthetic application of highly stereoselective intramolecular α-amidoalkylation reactions[9] of cyclic α-hydroxylactams derived from *N*-phenethylimides for the synthesis of fused or substituted tetrahydroisoquinoline systems, such as emetine-like alkaloids.[10] We have also developed an intermolecular α-amidoalkylation approach of bicyclic α-hydroxylactams, generated by Parham cyclization, which offers an efficient alternative route to the isoquinoline alkaloids and other nitrogen-containing biologically active compounds.[9] Recent reports include organocatalytic enantioselective α-amidoalkylation reactions using chiral phosphoric acids as catalysts[11] (Figure 1).

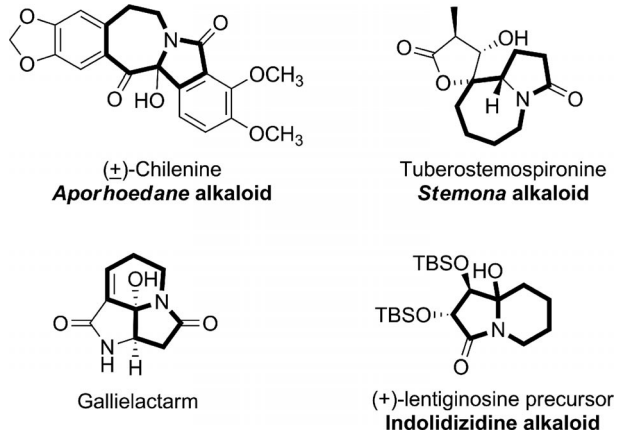


Figure 1. Selected bioactive polycyclic hydroxylactam derivatives.

On the other hand, the bicyclic α-hydroxy-γ-lactam framework is present in several natural products, or their immediate precursors, and therefore, the development of new synthetic procedures for the synthesis of these heterocycles continues to be an intensely investigated field. More precisely, the *Aporhoedane* alkaloids (e.g. Chilenine)[12] and *Stemona* alkaloids,[13] having a pyrrolo[1,2-*a*]azepine skeleton, as well as galiellalactone analogues[14] and the hydroxylated indolizidine alkaloids,[15] have interesting and potent biological activities including antiviral, antitumor, antitussive, and glucosidase inhibitory activity.

The potential utility of α-hydroxy-γ-lactams for natural products synthesis and medicinal chemistry led us to explore the construction of indolizidine and pyrroloazepine ring systems. In this context, we were attracted several years ago to the potential of olefin ring-closing metathesis (RCM)[16] for the assembly of complex target molecules (e.g. erythrinanes[17]) and medium-size nitrogen heterocycles.[18] RCM is now routinely applied to construct cyclic

[a] Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU,
Apdo. 644, 48080 Bilbao, Spain
E-mail: esther.lete@ehu.es
http://www.ehu.es

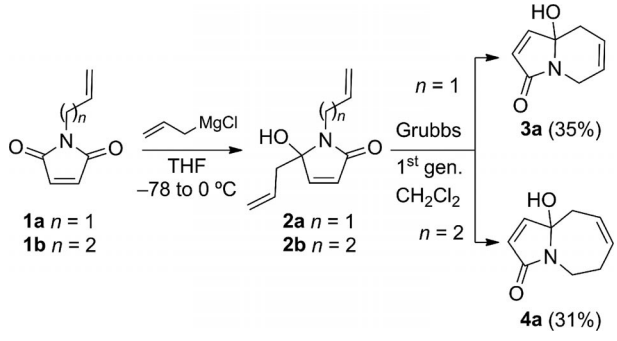
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300889.

olefins of virtually all ring sizes with a high degree of functional compatibility. However, there are few precedents of its application to substrates containing an α-hydroxylactam function. Thus, Kim et al.[19] have reported the synthesis of indolizidinones using RCM of *N*,5-hydroxy-α-hydroxylactams, though their preparation required the use of $PbBr_2$ in a zinc-mediated Barbier-type allylation. In a related approach, Huang[20] has described the construction of the five membered ring of indolizidine derivatives, starting from enantiopure piperidine building blocks, but the reaction product easily dehydrated.

We describe herein the combination of Grignard reagent addition to *N*-substituted imides with olefin ring-closing metathesis (RCM) as a strategy for the construction of six- or seven-membered azabicycles with polycyclic α-hydroxy-γ-lactam framework. The method was applied to the synthesis of enantiomerically pure compounds by using norborn-5-ene-2,3-dicarboxyimides with a 2-*exo*-hydroxybornylsulfinyl as chiral auxiliary to control diastereoselectivity.[21]

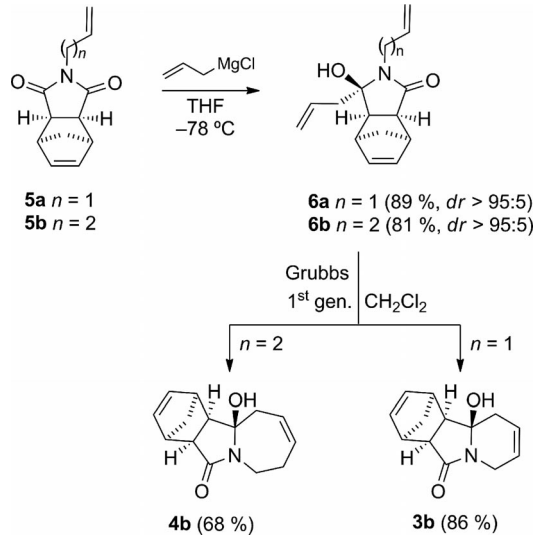
Results and Discussion

We started by studying the synthesis of 8a-hydroxyindolizinone **3a** and 9a-hydroxypyrrolo[1,2-*a*]azepinone **4a**. Thus, the *N*-allyl- or *N*-butenyl maleimides **1a**,**b** were treated with allylmagnesium chloride to afford corresponding hydroxylactams **2a**,**b**. These hydroxylactams were highly unstable, and were submitted to RCM conditions without further purification. Thus, both the six- and seven-membered rings could be obtained by this procedure using 4 mol-% of Grubbs' first-generation catalyst, though only in moderate yield (Scheme 1). The moderate overall yield could be attributed to the instability of the intermediate hydroxylactams. Although several reaction conditions were evaluated, the use of higher catalyst loading or longer reaction times did not improve the results.



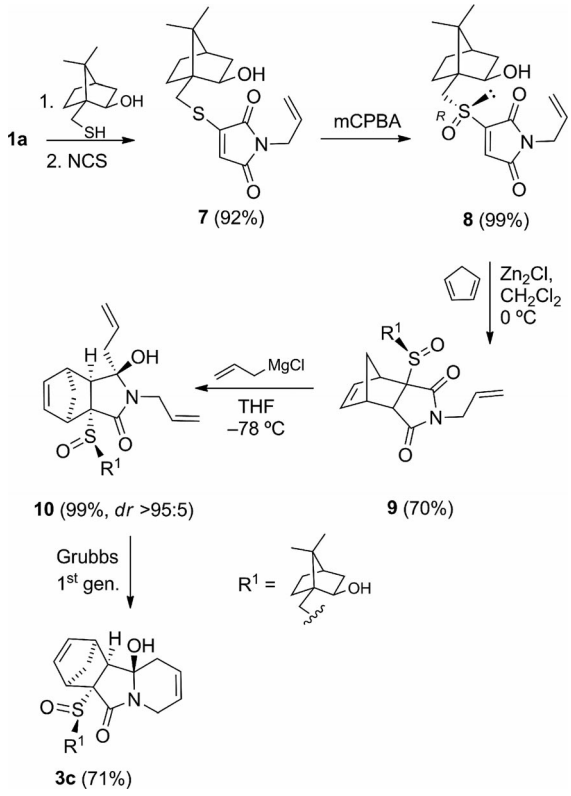
Scheme 1.

The same protocol was applied to norbornene dicarboxyimides **5a** and **5b**. As has been observed for related substrates,[9d] the ethylidene bridge of the norbornene moiety blocks one side of the imide carbonyl group. As a result, the addition of allylmagnesium chloride occurred with complete diastereoselectivity to give **6a** and **6b** as single diastereomers. These hydroxylactams were stable and could be fully characterized; they were subsequently submitted to RCM conditions using 4 mol-% of Grubbs' first-generation catalyst to afford 8a-hydroxyindolizinone **3b** and 9a-hydroxypyrrolo[1,2-*a*]azepinone **4b** in good yields (Scheme 2).



Scheme 2.

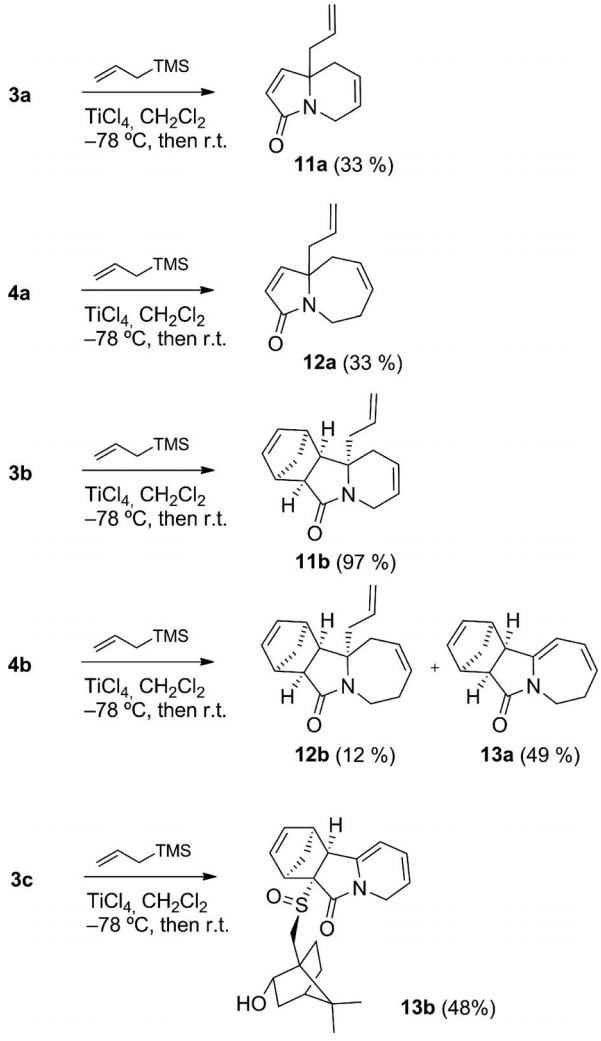
Having established that the allylmagnesium chloride addition/RCM sequence on norbornene dicarboxyimides proceeded with complete diastereoselectivity, we applied this procedure to the synthesis of an enantiomerically pure 8a-hydroxyindolizinone **3c**. For that purpose, we appended a 2-*exo*-hydroxy-10-bornylsulfinyl group to the norbornene moiety. The synthetic utility of this group was developed by Arai,[22] and has been applied by our group to the enantioselective synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines through inter- and intramolecular α-amidoalkylation reactions,[9d] and also as an activating group for conjugate addition reactions on the α,β-unsaturated amide moiety of this type of compounds.[23] Thus, our imide precursor would be (2-*exo*-hydroxy-10-bornyl)sulfinylnorbornene dicarboximide **9**, prepared as described in Scheme 3. Addition of 10-mercaptoisoborneol[24] to imide **1a** followed by treatment with NCS afforded maleimide **7**, which was oxidized with MCPBA to yield sulfinylmaleimide **8** as a single diastereoisomer in quantitative yield. As has been reported, the stereochemical outcome of this reaction is determined by the hydroxy group of the auxiliary.[25] The sulfoxide group controlled the stereochemistry of an asymmetric Diels–Alder reaction with cyclopentadiene in the presence of $ZnCl_2$ to obtain sulfinyl norbornene dicarboximide **9** in good yield (70%), as a single *endo* diastereoisomer.[26] The subsequent addition of allylmagnesium chloride occurred with complete diastereoselectivity. As stated before, the ethylidene bridge efficiently blocks the *Re* face of the carbonyl, leading to hydroxylactam **10** in quantitative yield. The RCM reaction carried out under the usual conditions gave enantiomerically pure 10b-hydroxypyridoisoindolone **3c** in high yield (Scheme 3).



Scheme 3.

Thus, the addition of allylmagnesium chloride to *N*-allyl or butenyl imides followed by RCM provides an efficient entry to fused pyrrolidine systems, with high diastereoselectivity. Although it has been reported that the presence of polar groups close to the double bonds[27] can inhibit RCM, in our case the metathesis proceeds smoothly in the presence of the free hydroxy group of the hydroxylactams.

These types of bicyclic hydroxylactams may also be further functionalized, as they are precursors of *N*-acyliminium intermediates. Indeed, the α-amidoalkylation reaction is a widely used method for C–C bond formation in heterocyclic chemistry and has found widespread application in natural products synthesis.[8] Although intermolecular α-amidoalkylation with *N*-acyliminium ions formed in situ from cyclic hydroxylactams to form tertiary or quaternary centers has been widely applied, there are very few examples of α-amidoalkylation of bicyclic *N*-acyliminium intermediates so far. In this context, we have previously shown that intermolecular α-amidoalkylation reaction with different π-nucleophiles (allylsilanes or enol ethers) can be accomplished upon treatment of bicyclic α-hydroxylactams, obtained by Parham cyclization, with Lewis acids to obtain nuevamine-type[1b] and dihydropyrroloisoquinoline alkaloids.[9d] With these precedents in mind, bicyclic α-hydroxy-γ-lactams **3a** and **4a** were submitted to intermolecular α-amidoalkylation conditions using allyltrimethylsilane as the π-nucleophile. After some experimentation, we found the best results were obtained by formation of the tertiary *N*-acyliminium ion using $TiCl_4$ as Lewis acid, followed by alkylation. Thus, corresponding allyl-substituted dihydroindolizinone **11a** and tetrahydropyrroloazepinone **12a** were obtained, though only in moderate yields (Scheme 4). When the reaction was applied to norbornene dicarboxyimide derived α-hydroxylactam **3b**, C-10b-substituted pyridoisoindolone **11b** was obtained in very good yield as a single diastereomer, with complete inversion of configuration at C-10b. However, when the procedure was applied to **4b**, only low yields of the azepinoisoindolone was obtained due to competitive dehydration, which afforded **13a** as the major reaction product. In a similar way, reaction of **3c** led to enantiomerically pure dehydrated pyridoisoindolone **13b** (Scheme 4). All attempts to improve yields by varying the reaction conditions or the identity of the nucleophile have thus far failed.



Scheme 4.

In the case of hydroxylactams **3b** and **4b**, the α-amidoalkylation reaction occurs with complete stereoselectivity, as a result of stereoelectronically favored axial attack of the nucleophile at the least hindered face of the *N*-acyliminium ion intermediate.[28] A thermal retro-Diels–Alder reaction was attempted to unmask the α,β-unsaturated amide moiety on **11b** and **12b**. Thus, these products were subjected to previously tested conditions for related substrates[9d,23]

(FVP at 500 °C and 1 Torr, or heating at reflux in *o*-dichlorobenzene). Unfortunately, only decomposition products were isolated under these conditions.

Nuclear Overhauser effect difference spectroscopy confirmed the stereochemistry of all hydroxylactams **3b**,**c**, **4b**, **6a**,**b** and their derivatives **11b** and **12b**. As an example, the most significant results obtained with **3c** and **11b** are shown in Figure 2. For hydroxylactam **3c**, NOE difference spectroscopy showed an enhancement between H-9 and the hydroxy group on C-10b. On the other hand, for **11b**, the absence of an NOE enhancement between allylic protons on C-10b and H-9 and the enhancement observed between methylene protons on C-10b and H-9 confirmed that the allyl substituent is on the opposite site to the methylidene C-9 – C-10 bridge. The rest of the NOE experiments carried out were fully consistent with the proposed stereochemistry in each case.

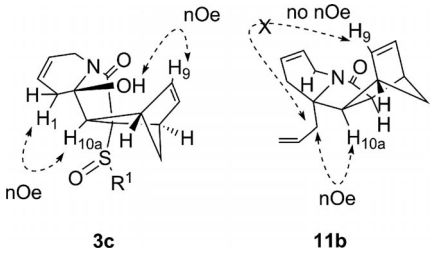
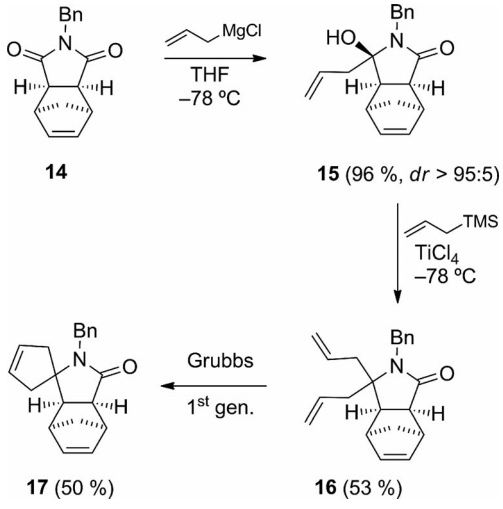


Figure 2. Observed critical NOE relationships for **3c** and **11b**.

A related protocol could be applied for the synthesis of spiro compounds using sequential introduction of two allyl groups in the same carbon atom. As outlined in Scheme 5, allylmagnesium addition to norbornene dicarboxyimide **14**, followed by intermolecular α-amidoalkylation reaction (allyltrimethylsilane, $TiCl_4$) to introduce the second allyl group, and subsequent RCM led to spiro derivative **17** in good overall yield. Unfortunately, attempts to carry out a retro-Diels–Alder reaction led to decomposition. These types of spirocyclic derivatives have been the targets of many synthetic efforts due to their utility as advanced intermediates



Scheme 5.

for the synthesis of *Cephalotaxus* alkaloids.[29] In fact, one of the most common strategies for the construction of the ABCD ring system of *Cephalotaxus* alkaloids, pioneered by Semmelhack and co-workers,[30] relies on B-ring formation by starting from a spirocyclic precursor.[31]

Conclusions

In summary, the allylmagnesium chloride addition/RCM sequence on *N*-alkenyl-substituted imides provides mild access to indolizinone and pyrroloazepinone derivatives with an α-hydroxylactam framework. This route compares quite favorably and effectively with other methods described in the literature.[32] When norbornene dicarboxyimides are used as substrates, the addition reactions are completely diastereoselective. Consequently, the procedure can be applied to the asymmetric synthesis of related derivatives, by employing a 2-*exo*-hydroxy-10-bornylsulfinyl group as a chiral auxiliary. The auxiliary controls the configuration at sulfur, which, in turn, determines the formation of the *endo* adduct in a chelation-controlled Diels–Alder reaction; the ethylidene bridge of the norbornene moiety is responsible for the stereochemical control in the addition reaction. Further functionality can be introduced at the angular position using an α-amidoalkylation reaction, though, in some cases in low yields, due to a competitive dehydration process. On the other hand, when the starting point is *N*-benzyl-substituted imide and an α-amidoalkylation reaction is performed prior to the RCM, azaspiro[4,4]nonane derivatives can be synthesized.

Experimental Section

General Methods: Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained in film over NaCl pellets or KBr pellets. NMR spectra were recorded at 20–25 °C, at 300 MHz for ^1H and 75.5 MHz for ^{13}C or at 500 MHz for ^1H and 125.7 MHz for ^{13}C in $CDCl_3$ solutions. Assignments of individual ^{13}C and ^1H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Selective NOE or NOESY experiments were performed when necessary. Mass spectra were recorded using electron impact (EI) at 70 eV, under chemical ionization (CI) at 230 eV. Exact mass was obtained using a TOF detector. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography was performed on silica gel (230–400 mesh) or on alumina (70–230 mesh).[33] All solvents used in reactions were anhydrous and purified according to standard procedures.[34] All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

Synthesis of Imides 1a-b, 5a–b and 14. General Procedure: A solution of the corresponding amine (1 mmol) and the anhydride (1–1.8 mmol) in glacial AcOH was heated under reflux for 5–16 h. The AcOH was removed under reduced pressure. CH_2Cl_2 (10 mL) and H_2O (20 mL) were added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 10 mL). The organic phase was washed with H_2O (3× 20 m). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in

vacuo. Flash column chromatography or crystallization afforded the imides **1a**–**b**, **5a**–**b** and **14**.

***N*-Allylmaleimide (1a):** According to the general procedure, a solution of *N*-allylamine (1.82 g, 31.29 mmol) and maleic anhydride (5.58 g, 56.32 mmol) in glacial AcOH (60 mL) was heated under reflux for 5 h. After work-up, flash column chromatography (silica gel, 40% hexane/AcOEt) afforded maleimide **1a** (3.00 g, 70%): m.p. (hexane): 44–46 °C (Lit.[35] m.p. 42–43) °C. IR (KBr): $\tilde{\nu}$ = 1702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.08 (dt, J = 5.6, 1.4 Hz, 2 H, $CH_2CH{=}CH_2$), 5.10–5.16 (m, 2 H, $CH_2CH{=}CH_2$), 5.76 (ddt, J = 17.2, 10.1, 5.6 Hz, 1 H, $CH_2CH{=}CH_2$), 6.69 (s, 2 H, H^2, H^3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 39.8 ($CH_2CH{=}CH_2$), 117.5 ($CH_2CH{=}CH_2$), 131.5 ($CH_2CH{=}CH_2$), 134.2 (C^2, C^3), 170.3 (C^1, C^4) ppm. MS (230 eV, CI): *m*/*z* (%) = (100) $[M + H]^+$, 137 (11) $[M]^+$, 110 (6). HRMS (CI) Calcd. for $C^7H_8NO_2$ $[M + H]^+$: 138.0555, found 138.0550. $C_7H_7NO_2$ (137.14): calcd. C 61.31, H 5.14, N 10.21; found C 61.31, H 5.15, N 9.96.

***N*-(3-Butenyl)maleimide (1b):** According to the general procedure, a solution of *N*-(3-butenyl)amine (1.06 g, 13.41 mmol) and maleic anhydride (2.39 g, 24.14 mmol) in glacial AcOH (30 mL) was heated under reflux for 16 h. After the work-up, flash column chromatography (silica gel, 40% hexane/AcOEt) afforded maleimide **1b**, whose data coincide with those previously reported[36] (1.24 g, 61%): IR (NaCl): $\tilde{\nu}$ = 1707 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.25 (q, J = 7.0 Hz, 2 H, $CH_2CH_2CH{=}CH_2$), 3.50 (t, J = 7.0 Hz, 2 H, $CH_2CH_2CH{=}CH_2$), 4.91–4.98 (m, 2 H, $CH_2CH_2CH{=}CH_2$), 5.63 (ddt, J = 17.1, 10.2, 7.0 Hz, 1 H, $CH_2CH_2CH{=}CH_2$), 6.61 (s, 2 H, H^2, H^3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.5 ($CH_2CH_2CH{=}CH_2$), 36.9 ($CH_2CH_2CH{=}CH_2$), 117.3 ($CH_2CH_2CH{=}CH_2$), 133.8, 134.2 ($CH_2CH_2CH{=}CH_2$, C^2, C^3), 170.5 (C^1, C^4) ppm. MS (230 eV, CI): *m*/*z* (%) = 152 (2) $[M + H]^+$, 137 (29), 135 (95), 132 (94), 97 (17), 89 (10), 88 (13), 87 (58), 86 (70), 85 (91), 84 (100), 83 (18). HRMS (CI) Calcd. for $C_8H_{10}NO_2$ $[M + H]^+$: 152.0712, found 152.0713.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-2-Allyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindole-1,3(2*H*)-dione (5a): According to the general procedure, a solution of *N*-allylamine (0.66 g, 11.30 mmol) and *cis*-norborn-5-en-*endo*-2,3-dicarboxylic anhydride (1.90 g, 11.30 mmol) in AcOH glacial (20 mL) was heated under reflux for 16 h. After the work-up, crystallization from MeOH afforded imide **5a** (2.20 g, 99%): m.p. (MeOH): 55–57 °C. IR (KBr): $\tilde{\nu}$ = 1696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, J = 8.8 Hz, 1 H, H^8), 1.72 (d, J = 8.8 Hz, 1 H, H^8), 3.24–3.28 (m, 2 H, H^{3a}, H^{7a}), 3.37–3.40 (m, 2 H, H^4, H^7), 3.93 (dt, J = 5.9, 1.4 Hz, 2 H, $CH_2CH{=}CH_2$), 5.09–5.20 (m, 2 H, $CH_2CH{=}CH_2$), 5.64 (ddt, J = 17.1, 10.2, 5.9 Hz, 1 H, $CH_2CH{=}CH_2$), 6.09 (broad s, 2 H, H^5, H^6) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 40.5 ($CH_2CH{=}CH_2$), 44.9 (C^4, C^7), 45.8 (C^{3a}, C^{7a}), 52.2 (C^8), 118.1 ($CH_2CH{=}CH_2$), 130.9 ($CH_2CH{=}CH_2$), 134.5 (C^5, C^6), 177.2 (C^1, C^3) ppm. MS (230 eV, CI): *m*/*z* (%) = 204 (63) $[M + H]^+$, 203 (14) $[M]^+$, 166 (28), 138 (100). HRMS (CI) Calcd. for $C_{12}H_{14}NO_2$ $[M + H]^+$: 204.1025, found 204.1023. $C_{12}H_{13}NO_2$ (203.24): calcd. C 70.92, H 6.45, N 6.89; found C 71.11, H 6.49, N 7.01.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-2-(But-3-en-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindole-1,3(2*H*)-dion3 (5b): According to general procedure, a solution of *N*-(3-butenyl)amine (0.39 g, 5.01 mmol) and *cis*-norborn-5-en-*endo*-2,3-dicarboxylic anhydride (0.85 g, 5.01 mmol) in glacial AcOH (20 mL) was heated under reflux for 16 h. After the work-up, crystallization in MeOH afforded imide **5b** (1.07 g, 99%), whose data coincide with those previously reported:[37] m.p. (MeOH): 58–60 °C. IR (KBr): $\tilde{\nu}$ = 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, J = 8.7 Hz, 1 H, H^8), 1.72 (d, J = 8.7 Hz, 1 H, H^8), 2.18 (q, J = 7.0 Hz, 2 H, $CH_2CH_2CH{=}CH_2$), 3.19–3.21 (m, 2 H, H^{3a}, H^{7a}), 3.36–3.41 (m, 4 H, $CH_2CH_2CH{=}CH_2$, H^4, H^7), 4.98–5.05 (m, 2 H, $CH_2CH_2CH{=}CH_2$), 5.66 (ddt, J = 17.0, 10.2, 7.0 Hz, 1 H, $CH_2CH_2CH{=}CH_2$), 6.03–6.06 (m, 2 H, H^5, H^6) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.0 ($CH_2CH_2CH{=}CH_2$), 37.7 ($CH_2CH_2CH{=}CH_2$), 44.8 (C^4, C^7), 45.7 (C^{3a}, C^{7a}), 52.2 (C^8), 117.2 ($CH_2CH_2CH{=}CH_2$), 134.4, 134.5 ($CH_2CH_2CH{=}CH_2$, C^5, C^6), 177.6 (C^1, C^3) ppm. MS (230 eV, CI): *m*/*z* (%) = 218 (29) $[M + H]^+$, 217 (18) $[M]^+$, 180 (25), 152 (100), 151 (21), 110 (9). HRMS (CI) Calcd. for $C_{13}H_{16}NO_2$ $[M + H]^+$: 218.1181, found 218.1174. $C_{13}H_{15}NO_2$ (217.27): calcd. C 71.87, H 6.96, N 6.45; found C 71.80, H 7.05, N 6.73.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-2-Benzyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindol-1,3(2*H*)-dione (14): According to general procedure, a solution of *N*-benzylamine (1.57 mL, 14.20 mmol) and *cis*-norborn-5-en-*endo*-2,3-dicarboxylic anhydride (2.40 g, 14.20 mmol) in glacial AcOH (20 mL) was heated under reflux for 5 h. After work-up, crystallization from MeOH afforded imide **14** (3.55 g, 99%), whose data are consistent with those previously reported:[38] m.p. (MeOH): 87–89 °C. IR (KBr): $\tilde{\nu}$ = 1696 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.48 (d, J = 8.8 Hz, 1 H, H^8), 1.66 (d, J = 8.8 Hz, 1 H, H^8), 3.21–3.24 (m, 2 H, H^{3a}, H^{7a}), 3.33–3.35 (m, 2 H, H^4, H^7), 4.46 (s, 2 H, NCH_2), 5.85–5.88 (m, 2 H, H^5, H^6), 7.23–7.28 (m, 5 H, H^{arom}) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 41.9 (NCH_2), 44.9 (C^4, C^7), 45.6 (C^{3a}, C^{7a}), 52.0 (C^8), 127.6, 128.3, 128.8 (HC_{arom}), 134.2 (C^5, C^6), 136.0 (CC^{arom}), 177.2 (C^1, C^3) ppm. MS (70 eV, EI): *m*/*z* (%) = 253 (3) $[M]^+$, 87 (6), 87 (7), 85 (53), 83 (100), 71 (5). HRMS (EI) Calcd. for $C_{16}H_{15}NO_2$ (M^+): 253.1103, found 253.1112.

8a-Hydroxy-8,8a-dihydroindolizin-3(5*H*)-one (3a): Allylmagnesium chloride (0.75 mL of a 2.0 M solution in THF, 1.5 mmol) was added dropwise to a solution of maleimide **1a** (170 mg, 1.25 mmol) in dry THF (10 mL) at –78 °C. The reaction mixture was warmed up to 0 °C and stirred for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo affording corresponding α-hydroxylactam **2a**. This intermediate, without purification, was dissolved in dry CH_2Cl_2 (0.01 M), and was treated with first-generation Grubb's catalyst (41 mg, 0.05 mmol, 4 mol-%) for 6 h at room temperature. Removal the solvent under reduced pressure, followed by flash column chromatography (silica gel, 80% hexane/AcOEt) afforded dihydroindolizinone **3a**[39] (63.2 mg, 35%): m.p. (AcOEt): 107–109 °C. IR (KBr): $\tilde{\nu}$ = 3290, 1680 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.27 (d, J = 17.3 Hz, 1 H, H^8), 2.57 (dd, J = 17.3, 3.4 Hz, 1 H, H^8), 3.59–3.64 (m, 1 H, H^5), 3.90 (broad s, 1 H, OH), 4.33 (dd, J = 18.2, 2.3 Hz, 1 H, H^5), 5.72–5.77 (m, 1 H, H^7), 5.80 (dd, J = 10.0, 2.3 Hz, 1 H, H^6), 6.03 (d, J = 5.9 Hz, 1 H, H^2), 7.07 (d, J = 5.9 Hz, 1 H, H^1) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 33.6 (C_8), 37.2 (C^5), 86.2 (C^{8a}), 120.7 (C^7), 122.6 (C^6), 126.2 (C^2), 150.1 (C^1), 167.7 (C^3) ppm. MS (230 eV, CI): *m*/*z* (%) = 152 (100) $[M + H]^+$, 151 (22) $[M]^+$, 136 (47), 135 (23), 134 (78), 133 (27), 132 (19). HRMS (CI) Calcd. for $C_8H_{10}NO_2$ $[M + H]^+$ 152.0712, found 152.0707. $C_8H_9NO_2$ (151.16): calcd. C 63.56, H 6.00, N 9.27; found C 63.51, H 6.03, N 8.95.

9a-Hydroxy-5,6,9,9a-tetrahydro-3*H*-pyrrolo[1,2-*a*]azepin-3-one (4a): According to the procedure described for the synthesis of **3a**, *N*-(3-butenyl)maleimide (**1b**) (390 mg, 2.55 mmol) was treated with allylmagnesium chloride (1.61 mL of a 2.0 M solution in THF, 3.07 mmol) and the first-generation Grubb's catalyst (0.13 g,

0.15 mmol). Purification by flash column chromatography (silica gel, AcOEt) afforded pyrroloazepinone **4a** (130 mg, 31%): IR (NaCl): $\tilde{\nu}$ = 3310, 1678 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.38 (m, 3 H, 2× H^6, H^9), 2.73 (dd, J = 15.1, 7.7 Hz, 1 H, H^9), 3.01–3.15 (m, 1 H, H^5), 3.89 (dt, J = 13.9, 4.1 Hz, 1 H, H^5), 4.06 (s, 1 H, OH), 5.59–5.66 (m, 1 H, H^8), 5.95–6.03 (m, 1 H, H^7), 5.97 (d, J = 5.8 Hz, 1 H, H^2), 6.86 (d, J = 5.8 Hz, 1 H, H^1) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.8 (C^6), 36.1 (C^5), 36.4 (C^9), 90.0 (C^{9a}), 123.9 (C^8), 126.1 (C^7), 133.3 (C^2), 150.3 (C^1), 169.1 (C^3) ppm. MS (230 eV, CI): m/z (%) = 166 (42) $[M + H]^+$, 165 (10) $[M]^+$, 150 (27), 149 (23), 148 (100), 147 (35). HRMS (CI) Calcd. for $C_9H_{12}NO_2$ $[M + H]^+$ 166.0868, found 166.0874. $C_9H_{11}NO_2$ (165.19): calcd. C 65.44, H 6.71, N 8.48; found C 65.69, H 6.77, N 8.08.

(3*RS*,3a*RS*,4*SR*,7*RS*,7a*SR*)-2,3-Diallyl-3-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoisoindol-1-one (6a): Allylmagnesium chloride (6.01 mL of a 2.0 M solution in THF, 11.42 mmol) was added dropwise to a solution of norbornene dicarboxyimide **5a** (930 mg, 4.57 mmol) in dry THF (50 mL) at –78 °C, and the reaction mixture was stirred at this temperature for 5 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 50% hexane/AcOEt) afforded α-hydroxylactam **6a** as a single diastereomer (1.00 g, 89%): m.p. (Et_2O): 80–82 °C. IR (KBr): $\tilde{\nu}$ = 3307, 1649 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.31 (d, J = 8.3 Hz, 1 H, H^8), 1.48 (d, J = 8.3 Hz, 1 H, H^8), 2.40 (dd, J = 14.0, 6.8 Hz, 1 H, C^3-C*H*HCH=CH_2), 2.47 (dd, J = 14.0, 7.6 Hz, 1 H, C^3-CH*H*CH=CH_2), 2.78 (dd, J = 8.9, 4.0 Hz, 1 H, H^{7a}), 2.95–2.98 (m, 2 H, H^{3a}, H^7), 3.14–3.19 (m, 1 H, H^4), 3.32, (s, 1 H, OH), 3.59 (dd, J = 15.5, 5.5 Hz, 1 H, NC*H*HCH=CH_2), 3.74 (dd, J = 15.5, 6.5 Hz, 1 H, NCH*H*CH=CH_2), 4.98 (d, J = 10.2 Hz, 1 H, NCH_2CH=C*H*H), 5.08–5.13 (m, 3 H, NCH_2CH=CH*H*, C^3-CH_2CH=C*H*$_2$), 5.54–5.63 (m, 1 H, C^3-CH_2C*H*=CH_2), 5.67–5.75 (m, 1 H, NCH_2C*H*=CH_2), 6.03 (dd, J = 5.3, 3.0 Hz, 1 H, H^5), 6.17 (dd, J = 5.3, 2.7 Hz, 1 H, H^6) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 41.0 (N*C*H_2CH=CH_2), 44.9 (C^7), 45.1 (C^3-*C*H_2CH=CH_2), 45.4 (C^4), 47.1 (C^{7a}), 48.9 (C^{3a}), 51.3 (C^8), 90.3 (C^3), 116.5 (NCH_2CH=*C*H_2), 119.7 (C^3-CH_2CH=*C*H_2), 131.5 (C^3-CH_2C*H*=CH_2), 134.3 (C^6), 134.4 (NCH_2C*H*=CH_2), 134.9 (C^5), 173.7 (C^1) ppm. MS (230 eV, CI): m/z (%) = 246 (100) $[M + H]^+$, 228 (35), 227 (14), 208 (39), 204 (53), 190 (11), 189 (13), 181 (10), 180 (92), 162 (43), 138 (27). HRMS (CI) Calcd. for $C_{15}H_{20}NO_2$ $[M + H]^+$: 246.1494, found 246.1486.

(3*RS*,3a*RS*,4*SR*,7*RS*,7a*SR*)-3-Allyl-2-(but-3-en-1-yl)-3-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoisoindol-1-one (6b): According to the procedure described for the synthesis of **6a**, allylmagnesium chloride (3.09 mL of a 1.9 M solution in THF, 5.87 mmol) was added dropwise to a solution of norbornene dicarboxyimide **5b** (510 mg, 2.35 mmol) in dry THF (50 mL) at –78 °C, and the reaction mixture was stirred at this temperature for 5 h. After the work-up, flash column chromatography (silica gel, 50% hexane/AcOEt) afforded α-hydroxylactam **6b** as a single diastereomer (500 mg, 81%): IR (NaCl): $\tilde{\nu}$ = 3308, 1649 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, J = 8.3 Hz, 1 H, H^8), 1.51 (d, J = 8.3 Hz, 1 H, H^8), 2.24 (q, J = 7.2 Hz, 2 H, CH_2CH_2CH=CH_2), 2.40 (dd, J = 13.9, 6.9 Hz, 1 H, C^3-C*H*HCH=CH_2), 2.47 (dd, J = 13.9, 7.6 Hz, 1 H, C^3-CH*H*CH=CH_2), 2.79 (dd, J = 8.9, 4.0 Hz, 1 H, H^{7a}), 2.86–2.92 (m, 2 H, C*H*HCH$_2$CH=CH_2, O*H*), 2.95–2.99 (m, 2 H, H^7, H^{3a}), 3.16–3.21 (m, 1 H, H^4), 3.31 (dt, J = 14.0, 7.2 Hz, 1 H, CH*H*CH$_2$CH=CH_2), 4.96–5.02 (m, 2 H, CH_2CH_2CH=C*H*$_2$), 5.10–5.15 (m, 2 H, C^3-CH_2CH=C*H*$_2$), 5.56–5.64 (m, 1 H, C^3-CH_2C*H*=CH_2), 5.67–5.73 (m, 1 H, CH_2CH_2C*H*=CH_2), 6.08 (dd, J = 5.4, 3.0 Hz, 1 H, H^5), 6.17 (dd, J = 5.4, 3.0 Hz, 1 H, H^6) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 33.2 (CH_2CH_2CH=CH_2), 38.6 (*C*H_2CH_2CH=CH_2), 44.8, 44.9 (C^7, *C*H_2CH=CH_2), 45.7 (C^4), 47.2 (C^{7a}), 49.1 (C^{4a}), 51.2 (C^8), 90.2 (C^3), 116.4 (CH_2CH_2CH=*C*H_2), 119.9 (C^3-CH_2CH=*C*H_2), 131.4 (C^3-CH_2C*H*=CH_2), 133.9 (C^6), 135.6 (C^5), 136.1 (CH_2CH_2C*H*=CH_2), 173.9 (C^1) ppm. MS (230 eV, CI): m/z (%) = 260 (100) $[M + H]^+$, 242 (37), 241 (16), 222 (36), 218 (59), 204 (10), 195 (11), 194 (80), 176 (40), 152 (50). HRMS (CI) Calcd. for $C_{16}H_{22}NO_2$ $[M + H]^+$: 260.1651, found 260.1662.

(6a*SR*,7*RS*,10*SR*,10a*RS*,10b*RS*)-10b-Hydroxy-1,6a,7,10,10a,10b-hexahydro-7,10-methanopyrido[2,1-*a*]isoindol-6(4*H*)-one (3b): A solution of α-hydroxylactam **6a** (110 mg, 0.44 mmol) in dry CH_2Cl_2 (0.01 *M*) was treated with first-generation Grubb's catalyst (14.60 mg, 0.02 mmol). The reaction mixture was stirred for 6 h at room temperature. Removal the solvent under reduced pressure, followed by flash column chromatography (silica gel, 90% hexane/AcOEt) afforded **3b** (83.00 mg, 86%): m.p. (AcOEt) 153–155 °C. IR (KBr): $\tilde{\nu}$ = 3340, 1667 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.41 (d, J = 8.4 Hz, 1 H, H^{11}), 1.58 (d, J = 8.4 Hz, 1 H, H^{11}), 2.26 (dd, J = 13.9, 3.7 Hz, 1 H, H^1), 2.46 (s, 1 H, OH), 2.45–2.51 (m, 1 H, H^1), 2.77 (dd, J = 9.1, 4.0 Hz, 1 H, H^{10a}), 3.10–3.12 (m, 1 H, H^{10}), 3.13 (dd, J = 9.1, 4.8 Hz, 1 H, H^{6a}), 3.26–3.27 (m, 1 H, H^7), 3.36–3.40 (m, 1 H, H^4), 4.20 (dd, J = 17.6, 1.8 Hz, 1 H, H^4), 5.62–5.68 (m, 2 H, H^2, H^3), 6.15 (dd, J = 5.5, 3.1 Hz, 1 H, H^8), 6.26 (dd, J = 5.5, 2.8 Hz, 1 H, H^9) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 37.2 (C^4), 39.6 (C^1), 44.8 (C^{10}), 45.4 (C^7), 49.6 (C^{6a}, C^{10a}), 51.9 (C^{11}), 85.0 (C^{10b}), 122.4, 123.2 (C^2, C^3), 134.3 (C^9), 135.4 (C^8), 171.6 (C^6) ppm. MS (230 eV, CI): m/z (%) = 218 (44) $[M + H]^+$, 200 (48), 199 (67), 198 (13), 180 (19), 162 (20), 152 (54), 134 (100), 133 (35), 132 (21). HRMS (CI) Calcd. for $C_{13}H_{16}NO_2$ $[M + H]^+$: 218.1181, found 218.1183. $C_{13}H_{15}NO_2$ (217.27): calcd. C 71.87, H 6.96, N 6.45; found C 72.27, H 6.89, N 6.24.

(1*SR*,4*RS*,4a*SR*,11a*RS*,11b*RS*)-11a-Hydroxy-4,4a,7,8,11,11a-hexahydro-1*H*-1,4-methanoazepino[2,1-*a*]isoindol-5(11b*H*)-one (4b): A solution of α-hydroxylactam **6b** (370 mg, 1.42 mmol) in dry CH_2Cl_2 (0.01 *M*) was treated with first-generation Grubb's catalyst (49.80 mg, 0.06 mmol). The reaction mixture was stirred for 6 h at room temperature. Removal the solvent under reduced pressure, followed by flash column chromatography (silica gel, AcOEt) afforded **4b** (220 mg, 68%): m.p. (AcOEt) 113–115 °C. IR (KBr): $\tilde{\nu}$ = 3343, 1655 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, J = 8.3 Hz, 1 H, H^{12}), 1.52 (d, J = 8.3 Hz, 1 H, H^{12}), 2.16–2.19 (m, 2 H, H^8), 2.45 (d, J = 15.1 Hz, 1 H, H^{11}), 2.58–2.63 (m, 2 H, H^{11}, OH), 2.68–2.75 (m, 2 H, H^{11b}, H^7), 3.06–3.09 (m, 1 H, H^1), 3.16 (dd, J = 8.9, 4.7 Hz, 1 H, H^{4a}), 3.22–3.26 (m, 1 H, H^4), 3.81 (dt, J = 13.8, 3.7 Hz, 1 H, H^7), 5.62–5.67 (m, 1 H, H^{10}), 5.99–6.02 (m, 1 H, H^9), 6.04 (dd, J = 5.3, 3.0 Hz, 1 H, H^3), 6.13 (dd, J = 5.3, 2.7 Hz, 1 H, H^2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.3 (C^8), 35.8 (C^7), 44.6 (C^{11}), 45.0 (C^1), 45.4 (C^4), 49.1, 49.5 (C^{4a}, C^{11b}), 51.3 (C^{12}), 87.7 (C^{11a}), 122.5 (C^{10}), 134.4, 134.5, 134.6 (C^2, C^3, C^9), 172.3 (C^5) ppm. MS (230 eV, CI): m/z (%) = 232 (45) $[M + H]^+$, 231 (7) $[M]^+$, 214 (41), 213 (33), 194 (20), 176 (19), 166 (61), 164 (12), 149 (11), 148 (100), 147 (27). HRMS (CI) Calcd. for $C_{14}H_{18}NO_2$ $[M + H]^+$: 232.1338, found 232.1343.

(–)-1-Allyl-3-({[(1*R*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]-heptan-1-yl]methyl}thio)-1*H*-pyrrole-2,5-dione (7): To a solution of maleimide **1a** (490 mg, 3.56 mmol) in dry CH_2Cl_2 (400 mL) was added at 0 °C a solution of 10-mercaptoisoborneol (730 g, 3.91 mmol) and Et_3N (0.82 mL, 5.87 mmol) in dry CH_2Cl_2

(250 mL). The resulting mixture was stirred at this temperature for 30 min, and then at room temperature for 24 h. The solvent was removed under reduced pressure. The resulting crude reaction mixture was purified by flash column chromatography (silica gel, 40% hexane/AcOEt) to afford the addition product as a 1:1 ratio of diastereomers (1.01 g, 99% combined yield). The diastereomers could be separated and identified, but in subsequent reactions were used without separation. A solution of this mixture of diastereomers (2.30 g, 7.12 mmol) and NCS (1.07 g, 7.83 mmol) in dry CCl_4 (130 mL) was refluxed for 16 h. The solvent was concentrated in vacuo. The resulting crude reaction mixture was purified by flash column chromatography (silica gel, 30% hexane/AcOEt) affording maleimide **7** (2.10 g, 92%): $[\alpha]_D^{20}$ = –30.13 (*c* = 0.25, $CHCl_3$); m.p. (AcOEt) 115–117 °C. IR (KBr): $\tilde{\nu}$ = 3490, 1702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.07–1.12 (m, 1 H, H$^{5'}$), 1.25 (ddd, *J* = 13.0, 9.4, 4.0 Hz, 1 H, H$^{6'}$), 1.58–1.63 (m, 1 H, H$^{6'}$), 1.72–1.85 (m, 4 H, 2 × H$^{3'}$, H$^{4'}$, H$^{5'}$), 1.97 (broad s, 1 H, OH), 2.84 (d, *J* = 11.2 Hz, 1 H, SC*H*H), 3.23 (d, *J* = 11.2 Hz, 1 H, SCH*H*), 3.90 (dd, *J* = 7.5, 3.6 Hz, 1 H, H$^{2'}$), 4.11 (d, *J* = 5.7 Hz, 2 H, CH_2CH=CH$_2$), 5.15–5.20 (m, 2 H, CH$_2$CH=CH_2), 5.79 (ddd, *J* = 15.9, 10.8, 5.7 Hz, 1 H, CH$_2$C*H*=CH$_2$), 6.16 (s, 1 H, H^4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.0 (CH_3), 20.7 (CH_3), 27.0 (C$^{5'}$), 30.9 (C$^{6'}$), 31.7 (SCH_2), 40.1 (*C*H$_2$CH=CH$_2$), 40.4 (C$^{3'}$), 45.3 (C$^{4'}$), 48.2 (C$^{7'}$), 51.6 (C$^{1'}$), 76.5 (C$^{2'}$), 117.7, 117.8 (C^4, CH$_2$CH=*C*H$_2$), 131.5 (CH$_2$*C*H=CH$_2$), 151.8 (C^3), 167.5, 169.1 (C^2, C^5) ppm. MS (230 eV, CI): *m*/*z* (%) = 322 (51) [M + H]$^+$, 305 (10), 304 (46), 198 (7), 170 (8), 169 (14), 153 (8), 136 (11), 135 (100), 109 (6). HRMS (CI) Calcd. for $C_{17}H_{24}NO_3S$ [M + H]$^+$: 322.1477, found 322.1480. $C_{17}H_{23}NO_3S$ (321.43): calcd. C 63.52, H 7.21, N 4.36; found C 63.37, H 7.21, N 4.30.

(–)-1-Allyl-3-((*R*)-{[(1*R*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl]methyl}sulfinyl)-1*H*-pyrrole-2,5-dione (8): A solution of *m*-CPBA (1.42 g, 8.22 mmol) in dry CH_2Cl_2 (200 mL) was added at 0 °C to a solution of maleimide **7** (2.03 g, 6.32 mmol) in dry CH_2Cl_2 (200 mL). The mixture was warmed up to room temperature, and was stirred for 3 h. The reaction mixture was cooled to –78 °C, and the precipitate was filtered at this temperature. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 30 mL) and then brine (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo, to afford maleimide **8** (2.12 g, 99%): $[\alpha]_D^{20}$ = –31.87 (*c* = 0.25, $CHCl_3$). IR (NaCl): $\tilde{\nu}$ = 3470, 1707 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.19–1.27 (m, 1 H, H$^{5'}$), 1.56–1.60 (m, 1 H, H$^{6'}$), 1.70–1.89 (m, 5 H, 2 × H$^{3'}$, H$^{4'}$, H$^{5'}$), 3.09 (d, *J* = 12.9 Hz, 1 H, OSC*H*H), 3.38 (broad s, 1 H, OH), 3.50 (d, *J* = 12.9 Hz, 1 H, OSCH*H*), 4.08–4.10 (m, 1 H, H$^{2'}$), 4.14–4.18 (m, 2 H, CH_2CH=CH$_2$), 5.23–5.30 (m, 2 H, CH$_2$CH=CH_2), 5.81 (ddt, *J* = 16.2, 10.8, 5.4 Hz, 1 H, CH$_2$C*H*=CH$_2$), 7.17 (s, 1 H, H^4) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.8 (CH_3), 20.5 (CH_3), 27.1 (C$^{5'}$), 30.5 (C$^{6'}$), 38.7 (C$^{3'}$), 39.6 (*C*H$_2$CH=CH$_2$), 44.7 (C$^{4'}$), 48.7 (C$^{7'}$), 51.8 (C$^{1'}$), 55.8 (CH$_2$SO), 76.7 (C$^{2'}$), 118.8 (CH$_2$CH=*C*H$_2$), 130.7 (CH$_2$*C*H=CH$_2$), 133.4 (C^4), 154.6 (C^3), 165.9, 166.2 (C^2, C^5) ppm. MS (70 eV, EI): *m*/*z* (%) = 335 (8), 322 (27), 320 (23), 304 (24), 282 (18), 185 (36), 184 (12), 169 (26), 167 (48), 151 (26), 135 (100), 133 (19), 109 (24), 107 (53), 93 (11). $C_{17}H_{23}NO_4S$ (337.43): calcd. C 60.51, H 6.87, N 4.15; found C 60.23, H 6.72, N 3.83.

(–)-(3a*R*,4*R*,7*S*,7a*S*)-2-Allyl-3a-((*R*)-{[(1*R*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl]methyl}sufinyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoisoindole-1,3(2*H*)-dione (9): To a solution of maleimide **8** (2.14 g, 6.36 mmol) in dry CH_2Cl_2 (400 mL) was added at 0 °C $ZnCl_2$ (1.94 g, 13.98 mmol), and the mixture was stirred for 30 min. Cyclopentadiene (10 mmol) was added, and the reaction was stirred at 0 °C for 2 h. The reaction was quenched by the addition of 1 M HCl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash column chromatography (silica gel, 50% hexane/AcOEt, 2% EtN_3) afforded imide **9** (1.77 g, 70%): $[\alpha]_D^{20}$ = –24.10 (*c* = 0.25, $CHCl_3$); m.p. (pentane): 113–116 °C. IR (KBr): $\tilde{\nu}$ = 3449, 1698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.14–1.19 (m, 1 H, H$^{5'}$), 1.45 (ddd, *J* = 12.2, 9.1, 3.5 Hz, 1 H, H$^{6'}$), 1.50–1.56 (m, 1 H, H$^{6'}$), 1.74–1.88 (m, 5 H, 2 × H$^{3'}$, H$^{4'}$, H$^{5'}$, H^8), 2.28 (d, *J* = 9.2 Hz, 1 H, H^8), 3.02 (d, *J* = 12.8 Hz, 1 H, OSC*H*H), 3.43 (d, *J* = 12.8 Hz, 1 H, OSCH*H*), 3.47–3.49 (m, 2 H, H^{7a}, H^7), 3.57 (d, *J* = 3.3 Hz, 1 H, OH), 3.80–3.84 (m, 1 H, H^4), 3.97–4.03 (m, 3 H, H$^{2'}$, CH_2CH=CH$_2$), 5.16–5.29 (m, 2 H, CH$_2$CH=CH_2), 5.66 (ddt, *J* = 16.5, 10.5, 6.1 Hz, 1 H, CH$_2$C*H*=CH$_2$), 6.26–6.28 (m, 1 H, H^5), 6.33 (dd, *J* = 5.5, 2.6 Hz, 1 H, H^6) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.9 (CH_3), 20.5 (CH_3), 27.1 (C$^{5'}$), 30.8 (C$^{6'}$), 38.6 (C$^{3'}$), 41.1 (*C*H$_2$CH=CH$_2$), 45.0 (C$^{4'}$), 45.4 (C^7), 45.8 (C^4), 48.4 (C^{7a}), 49.4 (C$^{7'}$), 50.0, 50.1 (C^8, CH$_2$SO), 51.1 (C$^{1'}$), 71.5 (C^{3a}), 76.7 (C$^{2'}$), 119.1 (CH$_2$CH=*C*H$_2$), 130.1 (CH$_2$*C*H=CH$_2$), 136.2 (C^5), 138.7 (C^6), 172.0, 174.0 (C^1, C^3) ppm. MS (230 eV, CI): *m*/*z* (%) = 404 (24) [M + H]$^+$, 403 (2) [M]$^+$, 388 (9), 387 (23), 386 (93), 320 (9), 252 (16), 251 (33), 230 (9), 185 (23), 136 (11), 135 (100), 107 (6). HRMS (CI) Calcd. for $C_{22}H_{30}NO_4S$ [M + H]$^+$: 404.1896, found 404.1893. $C_{22}H_{29}NO_4S$ (403.54): calcd. C 65.48, H 7.24, N 3.47; found C 65.79, H 7.19, N 3.65.

(+)-(3*R*,3a*S*,4*S*,7*R*,7a*R*)-2,3-Diallyl-3-hydroxy-7a-((*R*)-{[(1*R*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl]methyl}sulfinyl)-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoisoindol-1-one (10): Allylmagnesium chloride (5.35 mL of a 1.9 M solution in THF, 10.15 mmol) was added dropwise to a solution of imide **9** (1.64 g, 4.07 mmol) in dry THF (50 mL) at –78 °C, and the reaction mixture was stirred at this temperature for 5 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (50% hexane/AcOEt) afforded α-hydroxylactam **10** (1.69 g, 99%): $[\alpha]_D^{20}$ = +21.60 (*c* = 0.5, $CHCl_3$). IR (NaCl): $\tilde{\nu}$ = 3350, 1660 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H, CH_3), 1.13–1.16 (m, 1 H, H$^{5'}$), 1.16 (s, 3 H, CH_3), 1.40–1.45 (m, 1 H, H$^{6'}$), 1.51–1.58 (m, 2 H, H$^{6'}$, H^8), 1.73–1.88 (m, 4 H, 2 × H$^{3'}$, H$^{4'}$, H$^{5'}$), 2.13 (d, *J* = 8.7 Hz, 1 H, H^8), 2.38 (dd, *J* = 14.0, 7.1 Hz, 1 H, C^3-C*H*HCH=CH$_2$), 2.52 (s, 1 H, C^3-OH), 2.66 (dd, *J* = 14.0, 7.3 Hz, 1 H, C^3-CH*H*CH=CH$_2$), 3.06–3.10 (m, 1 H, H^7), 3.37 (d, *J* = 13.1 Hz, 1 H, OSC*H*H), 3.41 (d, *J* = 4.0 Hz, 1 H, H^{3a}), 3.46 (d, *J* = 13.1 Hz, 1 H, OSCH*H*), 3.72–3.77 (m, 4 H, H^4, NCH_2CH=CH$_2$, C$^{2'}$-OH), 4.02 (m, 1 H, H$^{2'}$), 5.09–5.15 (m, 2 H, NCH$_2$CH=CH_2), 5.30 (m, 2 H, C^3-CH$_2$CH=CH_2), 5.68–5.76 (m, 1 H, NCH$_2$C*H*=CH$_2$), 5.80–5.89 (m, 1 H, C^3-CH$_2$C*H*=CH$_2$), 6.25 (dd, *J* = 5.3, 3.4 Hz, 1 H, H^5), 6.47 (dd, *J* = 5.3, 2.7 Hz, 1 H, H^6) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 20.0 (CH_3), 20.5 (CH_3), 27.1 (C$^{5'}$), 30.8 (C$^{6'}$), 38.5 (C$^{3'}$), 41.8 (N*C*H$_2$CH=CH$_2$), 44.9 (C$^{4'}$), 45.1 (C^7), 46.0 (C^3-*C*H$_2$CH=CH$_2$), 46.2 (C^4), 48.3 (C$^{7'}$), 49.8, 49.9 (C^8, CH$_2$SO), 50.7 (C^{3a}), 51.1 (C$^{1'}$), 74.6 (C^{7a}), 77.2 (C$^{2'}$), 89.3 (C^3), 117.0 (NCH$_2$CH=*C*H$_2$), 121.6 (C^3-CH$_2$CH=*C*H$_2$), 131.0 (C^3-CH$_2$*C*H=CH$_2$), 133.4 (NCH$_2$*C*H=CH$_2$), 136.2 (C^5), 139.5 (C^6), 167.8 (C^1) ppm. MS (230 eV, CI): *m*/*z* (%) = 446 (38) [M + H]$^+$, 429 (29), 428 (100), 411 (10), 410 (41), 362 (23), 344 (12), 294 (31), 293 (25), 276 (11), 228 (12), 227 (26), 226 (26). HRMS (CI) Calcd.

for $C_{25}H_{36}NO_4S$ [M + H]$^+$: 446.2365, found 446.2354. $C_{25}H_{35}NO_4S$ (445.62): calcd. C 67.38, H 7.92, N 3.14; found C 67.75, H 7.90, N 3.14.

(+)-(6a*R*,7*R*,10*S*,10a*S*,10b*R*)-10b-Hydroxy-6a-((*R*)-{[(1*R*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl]methyl}sulfinyl)-1,6a,7,10,10a,10b-hexahydro-7,10-methanepyrido[2,1-*a*]isoindol-6(4*H*)-one (3c): A solution of α-hydroxylactam **10** (1.60 g, 3.84 mmol) in dry CH_2Cl_2 (0.01*M*) was treated with first-generation Grubb's catalyst (130 mg, 0.15 mmol, 4 mol-%). The reaction mixture was stirred for 6 h at room temperature. Removal the solvent under reduced pressure, followed by flash column chromatography (silica gel, 70% hexane/AcOEt) afforded indolizinone **3c** (1.14 g, 71%): $[\alpha]_D^{20}$ = +9.33 (*c* = 0.5, $CHCl_3$); m.p. (from AcOEt): 202–204 °C. IR (KBr): $\tilde{\nu}$ = 3390, 1678 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.13–1.16 (m, 1 H, H$^{5'}$), 1.37–1.42 (m, 1 H, H$^{6'}$), 1.50–1.56 (m, 1 H, H$^{6'}$), 1.58 (d, *J* = 8.6 Hz, 1 H, H^{11}), 1.71–1.76 (m, 3 H, H$^{3'}$, H$^{4'}$, H$^{5'}$), 1.82–1.86 (m, 1 H, H$^{3'}$), 2.11 (d, *J* = 8.6 Hz, 1 H, H^{11}), 2.46–2.57 (m, 2 H, H^1), 2.88 (broad s, 1 H, C^{10b}-OH), 3.19–3.22 (s, 1 H, H^{10}), 3.26 (d, *J* = 3.9 Hz, 1 H, H^{10a}), 3.38 (s, 2 H, CH_2SO), 3.44–3.48 (m, 1 H, H^4), 3.62–3.66 (m, 1 H, H^7), 3.85 (d, *J* = 2.5 Hz, 1 H, C$^{2'}$-OH), 3.97–3.99 (m, 1 H, H$^{2'}$), 4.14–4.18 (m, 1 H, H^4), 5.69–5.72 (m, 2 H, H^2, H^3), 6.22 (dd, *J* = 5.2, 3.4 Hz, 1 H, H^8), 6.51 (dd, *J* = 5.2, 2.7 Hz, 1 H, H^9) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.9 (CH_3), 20.5 (CH_3), 27.1 (C$^{5'}$), 30.9 (C$^{6'}$), 37.8 (C^4), 38.5 (C$^{3'}$), 40.0 (C^1), 44.6 (C^{10}), 45.0 (C$^{4'}$), 45.8 (C^7), 48.3 (C$^{7'}$), 49.6, 49.7 (C^{11}, CH_2SO), 51.1 (C$^{1'}$), 52.4 (C^{10a}), 75.7 (C^{6a}), 77.2 (C$^{2'}$), 83.8 (C^{10b}), 122.4, 123.1 (C^2, C^3), 135.1 (C^8), 140.5 (C^9), 165.6 (C^6) ppm. MS (230 eV, CI): *m*/*z* (%) = 418 (29) [M + H]$^+$, 401 (26), 400 (100), 382 (38), 334 (22), 316 (16), 265 (24), 248 (13), 216 (14), 199 (29), 198 (34), 135 (25). HRMS (CI) Calcd. for $C_{23}H_{32}NO_4S$ [M + H]$^+$: 418.2052, found 418.2042. $C_{23}H_{31}NO_4S$ (417.56): calcd. C 66.16, H 7.48, N 3.35; found C 66.08, H 7.61, N 3.29.

α-Amidoalkylation Reactions. General Procedure: To a solution of the corresponding α-hydroxylactam **3a**–**b**, **4a**–**b** (1 mmol) in dry CH_2Cl_2 (10 mL), allyltrimethylsilane (4 mmol) and $TiCl_4$ (2 mmol) were added sequentially at –78 °C. The reaction mixture was stirred 8 h at –78 °C, warmed up to room temperature, and stirred 24 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash column chromatography afforded **11a**–**b**, **12a**–**b**.

8a-Allyl-8,8a-dihydroindolizin-3(5*H*)-one (11a): According to general procedure, a solution of α-hydroxylactam **3a** (100 mg, 0.67 mmol) in dry CH_2Cl_2, was treated with allyltrimethylsilane (0.43 mL, 2.70 mmol) and $TiCl_4$ (0.15 mL, 1.35 mmol) at –78 °C. After the work-up, flash column chromatography (silica gel, AcOEt) afforded dihydroindolizinone **11a**[35] (38.70 mg, 33%): IR (NaCl): $\tilde{\nu}$ = 1683 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01–2.06 (m, 1 H, H^8), 2.29–2.34 (m, 1 H, H^8), 2.37 (d, *J* = 7.3 Hz, 2 H, C*H*$_2$CH=CH$_2$), 3.48 (ddd, *J* = 18.8, 3.7, 2.2 Hz, 1 H, H^5), 4.47 (ddd, *J* = 18.8, 3.7, 2.8 Hz, 1 H, H^5), 5.00–5.03 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.41–5.50 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.69–5.73 (m, 1 H, H^7), 5.75–5.79 (m, 1 H, H^6), 6.13 (d, *J* = 5.9 Hz, 1 H, H^2), 7.07 (d, *J* = 5.9 Hz, 1 H, H^1) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.4 (C^8), 37.6 (C^5), 38.0 (*C*H$_2$CH=CH$_2$), 63.6 (C^{8a}), 119.0 (CH$_2$CH=*C*H$_2$), 121.6 (C^7), 123.5 (C^6), 126.6 (C^2), 131.9 (CH$_2$*C*H=CH$_2$), 151.9 (C^1), 168.9 (C^3) ppm. MS (230 eV, CI): *m*/*z* (%) = (100) [M + H]$^+$, 176, 135 (4), 134 (32), 132 (2). HRMS (CI) Calcd. for $C^{11}H_{14}NO$ [M + H]$^+$: 176.1075, found 176.1060. $C_{11}H_{13}NO$ (175.23): calcd. C 75.40, H 7.48, N 7.99; found C 75.19, H 7.91, N 7.61.

(6a*SR*,7*RS*,10*SR*,10a*RS*,10b*RS*)-10b-Allyl-1,6a,7,10,10a,10b-hexahydro-7,10-methanopyrido[2,1-*a*]isoindol-6(4*H*)-one (11b): According to general procedure, a solution of α-hydroxylactam **3b** (120 mg, 0.56 mmol) in dry CH_2Cl_2, was treated with allyltrimethylsilane (0.36 mL, 2.23 mmol) and $TiCl_4$ (0.12 mL, 1.12 mmol) at –78 °C. After the work-up, flash column chromatography (silica gel, AcOEt) afforded **11b** (130 mg, 97%): IR (NaCl): $\tilde{\nu}$ = 1673 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 8.2 Hz, 1 H, H^{11}), 1.53 (d, *J* = 8.2 Hz, 1 H, H^{11}), 2.04–2.08 (m, 1 H, H^1), 2.12 (dd, *J* = 13.9, 8.0 Hz, 1 H, C*H*HCH=CH$_2$), 2.20–2.25 (m, 1 H, H^1), 2.38 (dd, *J* = 13.9, 6.7 Hz, 1 H, CH*H*CH=CH$_2$), 2.68 (dd, *J* = 8.7, 3.7 Hz, 1 H, H^{10a}), 2.92–2.96 (s, 1 H, H^{10}), 3.13 (dd, *J* = 8.7, 5.1 Hz, 1 H, H^{6a}), 3.16–3.20 (s, 1 H, H^7), 3.34 (d, *J* = 5.1 Hz, 1 H, H^4), 4.98–5.03 (m, 1 H, H^4), 5.05–5.10 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.60–5.72 (m, 3 H, CH$_2$C*H*=CH$_2$, H^2, H^3), 6.03 (dd, *J* = 5.6, 2.5 Hz, 1 H, H^9) 6.08 (dd, *J* = 5.6, 3.0 Hz, 1 H, H^8) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 32.2 (C^1), 38.2 (C^4), 44.4, 44.7, 44.9 (*C*H$_2$CH=CH$_2$, C^{10}, C^{6a}), 47.5 (C^{10a}), 49.7 (C^7), 51.2 (C^{11}), 59.6 (C^{10b}), 119.5 (CH$_2$CH=*C*H$_2$), 121.4, 123.0, 132.6 (CH$_2$*C*H=CH$_2$, C^2, C^3), 133.0 (C^9), 135.9 (C^8), 174.1 (C^6) ppm. MS (230 eV, CI): *m*/*z* (%) = 242 (100) [M + H]$^+$, 204 (34), 201 (11), 200 (59), 176 (90), 134 (39). HRMS (CI) Calcd. for $C_{16}H_{20}NO$ [M + H]$^+$: 242.1545, found 242.1546. $C_{16}H_{19}NO$ (241.33): calcd. C 79.63, H 7.94, N 5.80; found C 79.59, H 7.58, N 5.64.

9a-Allyl-5,6,9,9a-tetrahydro-3*H*-pyrrolo[1,2-*a*]azepin-3-one (12a): According to general procedure, a solution of α-hydroxylactam **4a** (49.50 mg, 0.30 mmol) in dry CH_2Cl_2, was treated with allyltrimethylsilane (0.19 mL, 1.20 mmol) and $TiCl_4$ (0.07 mL, 0.60 mmol) at –78 °C. After the work-up, flash column chromatography (silica gel, AcOEt) afforded pyrroloazepinone **12a** (12.40 mg, 22%): IR (NaCl): $\tilde{\nu}$ = 1680 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.16–2.19 (m, 1 H, H^9), 2.23–2.26 (m, 2 H, H^6), 2.44–2.55 (m, 3 H, H^9, C*H*$_2$CH=CH$_2$), 2.80–2.86 (m, 1 H, H^5), 4.25 (dt, *J* = 14.0, 3.8 Hz, 1 H, H^5), 5.04–5.09 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.45 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1 H, CH$_2$C*H*=CH$_2$), 5.67–5.72 (m, 1 H, H^8), 6.03–6.08 (m, 1 H, H^7), 6.13 (d, *J* = 5.9 Hz, 1 H, H^2), 6.91 (d, *J* = 5.9 Hz, 1 H, H^1) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.2 (C^6), 35.8 (C^9), 36.5, 36.8 (C^5, *C*H$_2$CH=CH$_2$), 68.1 (C^{9a}), 118.9 (CH$_2$CH=*C*H$_2$), 125.9, 126.0 (C^8, C^2), 131.7 (CH$_2$*C*H=CH$_2$), 133.5 (C^7), 152.1 (C^1), 169.8 (C^3) ppm. MS (230 eV, CI): *m*/*z* (%) = 190 (100) [M + H]$^+$, 148 (20), 135 (2). HRMS (CI) Calcd. for $C_{12}H_{16}NO$ [M + H]$^+$: 190.1232, found 190.1213.

(1*SR*,4*RS*,4a*SR*,11a*RS*,11b*RS*)-11a-Allyl-4,4a,7,8,11,11a-hexahydro-1*H*-1,4-methanoazepino[2,1-*a*]isoindol-5-(11b*H*)-one (12b) and (1*SR*,4*RS*,4a*SR*,11b*RS*)-4,4a,7,8-Tetrahydro-1*H*-1,4-methanoazepino[2,1-*a*]isoindol-5-(11b*H*)-one (13a): According to general procedure, a solution of α-hydroxylactam **4b** (0.10 g, 0.44 mmol) in dry CH_2Cl_2, was treated with allyltrimethylsilane (0.28 mL, 1.76 mmol) and $TiCl_4$ (0.10 mL, 0.88 mmol) at –78 °C. After the work-up, flash column chromatography (silica gel, AcOEt) afforded pyrroloazepinones **12a** (13.00 mg, 12%), and **13a** (45.50 mg, 49%). Data for **12a**: IR (NaCl): $\tilde{\nu}$ = 1665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 8.2 Hz, 1 H, H^{12}), 1.57 (d, *J* = 8.2 Hz, 1 H, H^{12}), 2.05–2.27 (m, 4 H, 2×H^8, H^{11}, C*H*HCH=CH$_2$), 2.41 (dd, *J* = 13.9, 6.9 Hz, 1 H, CH*H*CH=CH$_2$), 2.52 (d, *J* = 14.9 Hz, 1 H, H^{11}), 2.62 (dd, *J* = 8.9, 3.6 Hz, 1 H, H^{11b}), 2.66–2.71 (m, 1 H, H^7), 2.92–2.97 (m, 1 H, H^1), 3.12 (dd, *J* = 8.9, 5.1 Hz, 1 H, H^{4a}), 3.21–3.25 (m, 1 H, H^4), 3.94 (ddd, *J* = 14.0, 5.8, 2.3 Hz, 1 H, H^7), 5.09–5.13 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.58–5.67 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.72–5.77 (m, 1 H, H^9), 5.94–5.99 (m, 1 H, H^{10}), 6.14 (dd, *J* = 5.6, 3.0 Hz, 1

H, H^3), 6.19 (dd, J = 5.6, 2.6 Hz, 1 H, H^2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 27.8 (C^8), 35.1 (C^{11}), 37.2 (C^7), 42.1 ($CH_2CH=CH_2$), 45.1 (C^4), 45.2 (C^1), 46.9 (C^{11b}), 48.8 (C^{4a}), 52.4 (C^{12}), 64.0 (C^{11a}), 119.3 ($CH_2CH=CH_2$), 128.0 (C^9), 132.5 (C^{10}), 132.7 ($CH_2CH=CH_2$), 134.0 (C^2), 135.6 (C^3), 175.0 (C^5) ppm. MS (230 eV, CI): *m*/*z* (%) = 256 (100) $[M + H]^+$, 254 (6), 218 (17), 215 (10), 214 (75), 190 (25), 148 (26). HRMS (CI) Calcd. for $C_{17}H_{22}NO$ $[M + H]^+$: 256.1701, found 256.1690. Data for **13a**: IR (NaCl): $\tilde{\nu}$ = 1658 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40 (d, J = 8.5 Hz, 1 H, H^{12}), 1.55 (d, J = 8.5 Hz, 1 H, H^{12}), 2.31–2.32 (m, 2 H, H^8), 3.09 (dd, J = 8.4, 4.6 Hz, 1 H, H^{11b}), 3.12–3.15 (m, 1 H, H^1), 3.25–3.28 (m, 2 H, H^{4a}, H^4), 3.34–3.38 (m, 1 H, H^7), 3.70–3.73 (m, 1 H, H^7), 5.02 (d, J = 7.3 Hz, 1 H, H^{11}), 5.62–5.67 (m, 1 H, H^9), 5.74 (dd, J = 10.7, 7.3 Hz, 1 H, H^{10}), 6.01 (dd, J = 5.5, 2.8 Hz, 1 H, H^2), 6.05 (dd, J = 5.5, 2.7 Hz, 1 H, H^3) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.8 (C^8), 42.0, 42.1 (C^{4a}, C^7), 44.8 (C^4), 46.9, 47.3 (C^1, C^{11b}), 50.5 (C^{12}), 99.1 (C^{11}), 124.7 (C^{10}), 128.3 (C^9), 134.5, 134.6 (C^2, C^3), 145.3 (C^{11a}), 175.6 (C^5) ppm.

(–)-(6a*R*,7*R*,10*S*,10a*S*)-10b-Hydroxy-6a-((*R*)-{[(1*R*,2*R*,4*R*)-7,7-dimethylbicyclo[2.2.1]heptan-1-yl]methyl}sulfinyl)-1,6a,7,10-tetrahydro-7,10-methanepyrido[2,1-*a*]isoindol-6(4*H*)-one (13b): According to general procedure, a solution of α-hydroxylactam **3c** (180 mg, 0.43 mmol) in dry CH_2Cl_2, was treated with allyltrimethylsilane (0.27 mL, 1.71 mmol) and $TiCl_4$ (0.10 mL, 0.85 mmol) at –78 °C. After the work-up, flash column chromatography (silica gel, AcOEt) afforded **13b** (83 mg, 48%): $[\alpha]_D^{20}$ = –14.10 (c = 0.5, CH_3OH). IR (NaCl): $\tilde{\nu}$ = 3413, 1702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.11–1.16 (m, 1 H, $H^{5'}$), 1.40–1.45 (m, 1 H, $H^{6'}$), 1.50–1.56 (m, 1 H, $H^{6'}$), 1.58 (d, J = 8.6 Hz, 1 H, H^{11}), 1.72–1.77 (m, 3 H, $H^{3'}$, $H^{4'}$, $H^{5'}$), 1.82–1.86 (m, 1 H, $H^{3'}$), 2.13 (d, J = 8.6 Hz, 1 H, H^{11}), 3.16 (d, J = 12.9 Hz, 1 H, C*H*HSO), 3.36 (d, J = 12.9 Hz, 1 H, CH*H*SO), 3.52 (d, J = 4.2 Hz, 1 H, H^{10a}), 3.72 (s, 1 H, H^7), 3.76 (s, 1 H, $C^{2'}$-OH), 3.99–4.01 (m, 1 H, $H^{2'}$), 4.12–4.16 (m, 1 H, H^4), 4.32–4.36 (m, 1 H, H^4), 5.01 (d, J = 5.8 Hz, 1 H, H^1), 5.33–5.36 (m, 1 H, H^3), 5.78–5.82 (m, 1 H, H^2), 6.24 (dd, J = 5.4, 3.2 Hz, 1 H, H^8), 6.34 (dd, J = 5.4, 2.9 Hz, 1 H, H^9) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 19.9 (CH_3), 20.5 (CH_3), 27.1 ($C^{5'}$), 30.9 ($C^{6'}$), 38.5 ($C^{3'}$), 42.4 (C^4), 45.0, 45.2, 45.3 ($C^{4'}$, C^7, C^{10a}), 47.1 (C^{10}), 48.3 ($C^{7'}$), 49.6, 49.7 (C^{11}, CH_2SO), 51.1 ($C^{1'}$), 72.2 (C^{6a}), 77.1 ($C^{2'}$), 97.3 (C^1), 116.2 (C^3), 121.7 (C^2), 136.1 (C^8), 138.6 (C^9), 138.8 (C^{10b}), 169.0 (C^6) ppm. MS (230 eV, EI): *m*/*z* (%) = 399 (29) $[M]^+$, 389 (11), 388 (52), 386 (13), 370 (43), 368 (35), 353 (22), 352 (23), 351 (100), 335 (25), 183 (11), 127 (13).

(3*RS*,3a*RS*,4*SR*,7*RS*,7a*SR*)-3-Allyl-2-benzyl-3-hydroxy-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoisoindol-1-one (15): Allylmagnesium chloride (8.24 mL of a 1.9 M solution in THF, 15.65 mmol) was added dropwise to a solution of imide **14** (1.58 g, 6.26 mmol) in dry THF (40 mL) at –78 °C, and the reaction mixture was stirred at this temperature for 2 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Crystallization in hexane afforded α-hydroxylactam **15** (1.77 g, 96%): m.p. (hexane): 132–134 °C. IR (KBr): $\tilde{\nu}$ = 3300, 1649 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (d, J = 8.5 Hz, 1 H, H^8), 1.58 (d, J = 8.5 Hz, 1 H, H^8), 1.93 (s, 1 H, OH), 2.42–2.49 (m, 2 H, $CH_2CH=CH_2$), 2.90 (dd, J = 9.0, 3.9 Hz, 1 H, H^{3a}), 3.00–303 (m, 1 H, H^4), 3.15 (dd, J = 9.0, 4.7 Hz, 1 H, H^{7a}), 3.30–3.33 (m, 1 H, H^7), 4.16 (d, J = 15.1 Hz, 1 H, NC*H*H), 4.52 (d, J = 15.1 Hz, 1 H, NCH*H*), 5.08–5.15 (m, 2 H, $CH_2CH=CH_2$), 5.59 (ddt, J = 17.3, 10.2, 7.2 Hz, 1 H, $CH_2CH=CH_2$), 6.09 (dd, J = 5.3, 2.6 Hz, 1 H, H^5), 6.23 (dd, J = 5.3, 3.1 Hz, 1 H, H^6), 7.18–7.32 (m, 5 H, H^{arom}) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 42.3 (NCH_2), 44.8, 45.1 ($CH_2CH=CH_2$, C^4), 45.9 (C^7), 47.5 (C^{3a}), 49.1 (C^{7a}), 52.0 (C^8), 91.0 (C^3), 120.1 ($CH_2CH=CH_2$), 127.1, 128.2, 128.3 (HC_{arom}), 131.3 ($CH_2CH=CH_2$), 133.3 (C^5), 136.9 (C^6), 138.9 (CC^{arom}), 174.0 (C^1) ppm. MS (70 eV, EI): *m*/*z* (%) = 277 (6) $[M^+ – H_2O]$, 254 (29), 211 (63), 188 (39), 120 (11), 110 (32), 91 (100), 83 (11), 65 (19). HRMS (EI) Calcd. for $C_{19}H_{19}NO$ $[M^+ – H_2O]$: 227.1467, found 277.1468.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-3,3-Diallyl-2-benzyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoisoindol-1-one (16): According to the general procedure for α-amidoalkylation, α-hydroxylactam **15** (210 mg, 0.73 mmol) in dry CH_2Cl_2 (10 mL), was treated with allyltrimethylsilane (0.47 g, 2.90 mmol) and $TiCl_4$ (0.16 mL, 1.45 mmol) at –78 °C. After the work-up, flash column chromatography (silica gel, 50% hexane/AcOEt) afforded **16** (130 mg, 53%). IR (NaCl): $\tilde{\nu}$ = 1672 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (d, J = 8.3 Hz, 1 H, H^8), 1.55 (d, J = 8.3 Hz, 1 H, H^8), 2.07–2.16 (m, 2 H, $CH_2CH=CH_2$), 2.27–2.38 (m, 2 H, $CH_2CH=CH_2$), 2.55 (dd, J = 8.9, 3.5 Hz, 1 H, H^{3a}), 3.12–3.15 (m, 1 H, H^4), 3.17 (dd, J = 8.9, 4.9 Hz, 1 H, H^{7a}), 3.25–3.28 (m, 1 H, H^7), 3.81 (d, J = 15.7 Hz, 1 H, NC*H*H), 4.78 (d, J = 15.7 Hz, 1 H, NCH*H*), 5.02–5.12 (m, 4 H, 2× $CH_2CH=CH_2$), 5.58–5.66 (m, 1 H, $CH_2CH=CH_2$), 5.79–5.87 (m, 1 H, $CH_2CH=CH_2$), 6.04 (dd, J = 5.5, 2.7 Hz, 1 H, H^5), 6.26 (dd, J = 5.5, 2.9 Hz, 1 H, H^6), 7.17–7.26 (m, 5 H, H^{arom}) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 42.1 ($CH_2CH=CH_2$), 43.2 (NCH_2), 43.6 ($CH_2CH=CH_2$), 44.9 (C^7), 45.6 (C^4), 46.5 (C^{3a}), 49.4 (C^{7a}), 52.0 (C^8), 66.1 (C^3), 118.8, 119.7 (2× $CH_2CH=CH_2$), 126.8, 127.5, 128.1 (HC_{arom}), 132.4, 133.4 (2× $CH_2CH=CH_2$), 134.0 (C^5), 136.0 (C^6), 138.8 (CC^{arom}), 176.3 (C^1) ppm. MS (230 eV, CI): *m*/*z* (%) = 320 (100) $[M + H]^+$, 282 (27), 278 (45), 254 (50), 212 (24), 91 (9). HRMS (CI) Calcd. for $C_{22}H_{26}NO$ $[M + H]^+$: 320.2014, found 320.2011. $C_{22}H_{25}NO$ (319.45): calcd. C 82.72, H 7.89, N 4.38; found C 82.73, H 7.83, N 4.56.

(3a*SR*,4*RS*,7*SR*,7a*RS*)-2-Benzyl-3a,4,7,7a-tetrahydrospiro(4,7-methanoisoindol-1,1′-cyclopent-3-en)-3(2*H*)-one (17): A solution of **16** (85.00 mg, 0.25 mmol) in dry CH_2Cl_2 (0.01 *M*) was treated with first-generation Grubb's catalyst (8.0 mg, 0.01 mmol, 4%-mol). The reaction mixture was heated under reflux for 48 h. A second portion of the catalyst was added after heating for 24 h. The reaction was allowed to reach room temperature, and removal the solvent under reduced pressure, followed by flash column chromatography (silica gel, 50% hexane/AcOEt) afforded **17** (36.6 mg, 50%): m.p. (hexane/AcOEt): 94–96 °C. IR (KBr): $\tilde{\nu}$ = 1666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.36 (d, J = 8.3 Hz, 1 H, H^8), 1.55 (d, J = 8.3 Hz, 1 H, H^8), 2.07 (d, J = 17.5 Hz, 1 H, $H^{2'}$), 2.39 (d, J = 17.5 Hz, 1 H, $H^{2'}$), 2.46–2.50 (m, 2 H, $H^{5'}$), 2.75 (dd, J = 8.9, 3.8 Hz, 1 H, H^{7a}), 3.01–3.03 (m, 1 H, H^7), 3.27 (dd, J = 8.9, 4.8 Hz, 1 H, H^{3a}), 3.31–3.34 (m, 1 H, H^4), 3.81 (d, J = 15.2 Hz, 1 H, NC*H*H), 4.62 (d, J = 15.2 Hz, 1 H, NCH*H*), 5.56–5.57 (m, 1 H, $H^{3'}$), 5.66–5.67 (m, 1 H, $H^{4'}$), 5.90 (dd, J = 5.5, 2.5 Hz, 1 H, H^5), 6.24 (dd, J = 5.5, 2.8 Hz, 1 H, H^6), 7.16–7.23 (m, 5 H, H^{arom}) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 29.6 ($C^{2'}$), 40.0 (NCH_2), 43.4 (C^4), 45.4 (C^7), 46.7 (C^{3a}), 49.3, 49.4 ($C^{5'}$, C^{7a}), 51.0 (C^8), 70.4 (C^1), 126.7, 127.7, 127.8 (HC_{arom}), 128.6, 128.9 ($C^{3'}$, $C^{4'}$), 133.6 (C^5), 135.8 (C^6), 139.0 (CC^{arom}), 174.9 (C^3) ppm. MS (230 eV, CI): *m*/*z* (%) = (83) $[M + H]^+$, 292, 291 (21) $[M]^+$, 254 (36), 227 (16), 226 (100), 225 (19). HRMS (CI) Calcd. for $C_{20}H_{22}NO$ $[M + H]^+$: 292.1701, found 292.1699. $C_{20}H_{21}NO$ (291.39): calcd. C 82.44, H 7.26, N 4.81; found C 82.52, H 7.49, N 4.78.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of compounds described.

Acknowledgments

The authors wish to thank the Ministerio de Ciencia e Innovación (MICINN) (CTQ2009-07733), the Gobierno Vasco (IT-623-13) and the Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU (UFI11/22, GIU 09/46) for their financial support. Technical and human support provided by Servicios Generales de Investigación SGIker (UPV/EHU, MICINN, GV/EJ, ERDF and ESF) is gratefully acknowledged. The UPV/EHU is also thanked for a postdoctoral grant (to A. G.-S).

[1] For some selected examples of hydroxylactams as intermediates in synthesis of different type of alkaloids, see the following citations; lupine alkaloids: a) A. Consonni, B. Danieli, G. Lesma, D. Passarella, P. Piacenti, A. Silvani, *Eur. J. Org. Chem.* **2001**, 1377–1383; nuevamine-type alkaloids: b) I. Osante, E. Lete, N. Sotomayor, *Tetrahedron Lett.* **2004**, *45*, 1253–1256; c) A. Moreau, A. Couture, E. Deniau, P. Grandclaudon, *Eur. J. Org. Chem.* **2005**, 3437–3442; d) J. Selvakumar, C. R. Ramanathan, *Org. Biomol. Chem.* **2011**, *22*, 7643–7646; erythrinane alkaloids: e) S. Gao, Y. Q. Tu, X. Hu, S. Wang, R. Hua, Y. Jiang, Y. Zhao, X. Fan, S. Zhang, *Org. Lett.* **2006**, *8*, 2373–2376; f) F. Zhang, N. S. Simpkins, A. J. Blake, *Org. Biomol. Chem.* **2009**, *7*, 1963–1979; nicotine and analogs: g) S. Peixoto, T. M. Nguyen, D. Crich, B. Delpech, C. Marazano, *Org. Lett.* **2010**, *12*, 4760–4763.

[2] a) E. J. Corey, M. M. Mehrotra, *Tetrahedron Lett.* **1988**, *29*, 57–60; b) M. J. Moolenaar, W. N. Speckamp, H. Hiemstra, E. Poetsch, M. Casutt, *Angew. Chem.* **1995**, *107*, 2582; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2391–2393; c) M. Shimizu, Y. Nishigaki, A. Wakabayashi, *Tetrahedron Lett.* **1999**, *40*, 8873–8876; d) F. E. Chen, H. F. Dai, Y. Y. Kuang, H. Q. Jia, *Tetrahedron: Asymmetry* **2003**, *14*, 3667–3672; e) W. Bonrath, R. Karge, T. Netscher, F. Roessler, F. Spindler, *Chimia* **2009**, *63*, 265–269.

[3] E. Metais, L. E. Overman, M. I. Rodriguez, B. A. Stearns, *J. Org. Chem.* **1997**, *62*, 9210–9216.

[4] a) P. Lee, K. D. Moeller, *J. Am. Chem. Soc.* **1993**, *115*, 11434–11445; b) A. Reichelt, S. K. Bur, S. F. Martin, *Tetrahedron* **2002**, *58*, 6323–6328.

[5] a) D. Frehel, J.-P. Maffrand, *Heterocycles* **1983**, *20*, 1731–1735; b) J. H. Kim, Y. S. Lee, C. S. Kim, *Heterocycles* **1998**, *48*, 2279–2285; c) M. H. Todd, C. Ndubaku, P. A. Bartlett, *J. Org. Chem.* **2002**, *67*, 3985–3988.

[6] S. M. Allin, S. N. Gaskell, J. M. R. Towler, P. C. B. Page, B. Saha, M. J. McKenzie, W. P. Martin, *J. Org. Chem.* **2007**, *72*, 8972–8975.

[7] See, for example: a) H. Yoda, H. Kitayama, W. Yamada, T. Katagiri, K. Takabe, *Tetrahedron: Asymmetry* **1993**, *4*, 1451–1454; b) K. Matsuki, H. Inoue, A. Ishida, M. Takeda, M. Nakagawa, T. Hino, *Chem. Pharm. Bull.* **1994**, *42*, 9; c) M. D. Barker, R. A. Dixon, S. Jones, B. J. Marsh, *Tetrahedron* **2006**, *62*, 11663–11669; d) Z.-B. Ye, J. Chen, W.-H. Meng, P.-Q. Huang, *Tetrahedron: Asymmetry* **2010**, *21*, 895–902.

[8] For reviews on *N*-acyliminium ion chemistry, see: a) W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367–4416; b) H. Hiemstra, W. N. Speckamp, in: *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1988**, vol. 32, p. 271–339; c) H. Hiemstra, W. N. Speckamp, in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, UK, **1991**, vol. 2, p. 1047–1082; d) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856; e) B. E. Maryanoff, H. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431–1628; f) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 339–368; g) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 513–541; h) H. de Koning, W. N. Speckamp, in: *Stereoselective Synthesis (Houben–Weyl)* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, Germany, **1996**, workbench ed. E21, vol. 3, p. 1952–2010; i) S. T. Le Quement, R. Petersen, M. Meldal, T. E. Nielsen, *Biopolymers* **2010**, *94*, 242–256; j) U. Martínez-Estibalez, A. Gómez-SanJuan, O. García-Calvo, E. Aranzamendi, E. Lete, N. Sotomayor, *Eur. J. Org. Chem.* **2011**, 3610–3633.

[9] For some representative examples of our work, see: a) M. I. Collado, I. Manteca, N. Sotomayor, M. Villa, E. Lete, *J. Org. Chem.* **1997**, *62*, 2080–2092; b) I. Osante, M. I. Collado, E. Lete, N. Sotomayor, *Eur. J. Org. Chem.* **2001**, 1267–1277; c) A. Ardeo, E. Garcia, S. Arrasate, E. Lete, N. Sotomayor, *Tetrahedron Lett.* **2003**, *44*, 8445–8448; d) I. González-Temprano, I. Osante, E. Lete, N. Sotomayor, *J. Org. Chem.* **2004**, *69*, 3875–3885; e) E. García, S. Arrasate, A. Ardeo, E. Lete, N. Sotomayor, *Tetrahedron Lett.* **2001**, *42*, 1511–1513; f) E. García, S. Arrasate, E. Lete, N. Sotomayor, *J. Org. Chem.* **2005**, *70*, 10368–10374.

[10] E. Garcia, E. Lete, N. Sotomayor, *J. Org. Chem.* **2006**, *71*, 6776–6784.

[11] a) E. Aranzamendi, N. Sotomayor, E. Lete, *J. Org. Chem.* **2012**, *77*, 2986–2991; b) A. Gómez-SanJuan, N. Sotomayor, E. Lete, *Tetrahedron Lett.* **2012**, *53*, 2157–2159.

[12] For a recent review, see: M. S. Leonard, *ARKIVOC* **2013**, 1–65.

[13] For a recent review, see: R. A. Pilli, G. B. Rosso, M. C. Ferreira de Oliveira, *Nat. Prod. Rep.* **2010**, *27*, 1908–1937.

[14] J. Nilsson, R. Gidöf, M. Johansson, O. Sterner, *Tetrahedron* **2012**, *68*, 3336–3341, and references cited therein.

[15] J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139–165.

[16] For selected reviews on RCM, see: a) R. H. Grubbs, *Handbook of Metathesis*, Wiley, New York, **2003**; b) R. R. Schrock, *Angew. Chem.* **2006**, *118*, 3832; *Angew. Chem. Int. Ed.* **2006**, *45*, 3748–3759; c) R. H. Grubbs, *Angew. Chem.* **2006**, *118*, 3845; *Angew. Chem. Int. Ed.* **2006**, *45*, 3760–3765; d) J. C. Conrad, D. E. Fogg, *Curr. Org. Chem.* **2006**, *10*, 185–202; e) S. P. Nolan, H. Clavier, *Chem. Rev.* **2010**, *39*, 3305–3316. For selected reviews on RCM in natural products synthesis and medicinal chemistry, see: f) J. B. Brenneman, S. F. Martin, *Curr. Org. Chem.* **2005**, *9*, 1535–1549; g) M. Arisawa, A. Nishida, M. Nakagawa, *J. Organomet. Chem.* **2006**, *691*, 5109–5121; h) J. Cossy, S. Arseniyadis, C. Meyer (Eds.), *Metathesis in Natural Product Synthesis* Wiley-VCH, Weinheim, Germany, **2010**; i) M. J. Perez de Vega, M. I. García-Aranda, R. González-Muñiz, *Med. Res. Rev.* **2011**, *31*, 677–715.

[17] a) I. Osante, M. N. Abdullah, S. Arrasate, E. Lete, N. Sotomayor, *ARKIVOC* **2007**, *4*, 206–22; b) M. N. Abdullah, S. Arrasate, E. Lete, N. Sotomayor, *Tetrahedron* **2008**, *64*, 1323–1332.

[18] U. Martínez-Estíbalez, N. Sotomayor, E. Lete, *Tetrahedron Lett.* **2007**, *48*, 2919–2922.

[19] a) S. W. Kang, Y. H. Kim, S. H. Kim, *Bull. Korean Chem. Soc.* **2008**, *29*, 755–757; b) S. W. Kang, Y. H. Kim, H. J. Kim, J. H. Lee, S. H. Kim, *Bull. Korean Chem. Soc.* **2009**, *30*, 691–694.

[20] K. H. Zhang, X. Lin, H. Huang, P. Q. Huang, *Sci. China Chem.* **2011**, *54*, 737–744.

[21] This work was presented in part at the 9th International Symposium on Carbanion Chemistry (ISCC-9), Florence, Italy, July, **2010**; See book of abstracts: communication P-18.

[22] a) Y. Arai, M. Matsui, T. Koizumi, M. Shiro, *J. Org. Chem.* **1991**, *56*, 1983–1985; b) Y. Arai, M. Matsui, A. Fujii, T. Kontani, T. Ohno, T. Koizumi, M. Shiro, *J. Chem. Soc. Perkin Trans. 1* **1994**, 15–23.

[23] C. Camarero, I. González-Temprano, A. Gómez-SanJuan, S. Arrasate, E. Lete, N. Sotomayor, *Tetrahedron* **2009**, *65*, 5787–*5798*.

[24] Mercaptoisoborneol was prepared by $LiAlH_4$ reduction of commercial (1*S*)-(+)-10-camphorsulfonyl chloride according to literature procedure: E. L. Eliel, W. J. Frazee, *J. Org. Chem.* **1979**, *44*, 3598–3599.

[25] a) R. S. Glass, W. N. Setzer, U. D. G. Prahbu, G. S. Wilson, *Tetrahedron Lett.* **1982**, *23*, 2335–2338; b) O. de Lucchi, V. Lucchini, C. Marchioro, G. Valle, G. Modena, *J. Org. Chem.* **1986**,

51, 1457–1466; c) O. de Lucchi, V. Lucchini, C. Marchioro, G. Valle, G. Modena, *J. Org. Chem.* **1989**, *54*, 3245–3246. The stereochemical outcome of this kind of oxidation has also been explained through the formation of an intramolecular hydrogen bond, see: d) R. Annunziata, M. Cinquini, F. Cozzi, S. Farina, V. Montanari, *Tetrahedron* **1987**, *43*, 1013–1018.

[26] In the presence of $ZnCl_2$, formation of a zinc chelate with sulfinyl and carbonyl oxygen atoms would direct the attack of cyclopentadiene from the less hindered side to afford *endo* product **9**.

[27] See for example: T. J. Brocksom, U. Brocksom, D. Frederico, *Tetrahedron Lett.* **2004**, *45*, 9289–9891, and references cited therein.

[28] For reviews, see ref.[8] For some representative examples, see: a) C. Agami, F. Amiot, F. Couty, L. Dechoux, C. Kaminsky, O. Venier, *Tetrahedron: Asymmetry* **1998**, *9*, 3955–3958; b) H. Dhimane, C. Vanucci-Bacque', L. Hamon, G. Lhommet, *Eur. J. Org. Chem.* **1998**, 1955–1963; c) D. Potts, P. J. Stevenson, N. Thompson, *Tetrahedron Lett.* **2000**, *41*, 275–278; d) M. David, H. Dhimane, C. Vanucci-Bacque', L. Hamon, G. Lhommet, *Heterocycles* **2001**, *55*, 941–949.

[29] For selected reviews, see: a) M. A. J. Miah, T. Hudlicky, J. W. Reed, in: *The Alkaloids* (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, vol. 51, p. 199–269; b) T. Hudlicky, J. W. Reed, The *Way of Synthesis: Evolution of Design and Methods for Natural Products*, Wiley-VCH, Weinheim, Germany, **2007**, part 4.5, p. 655–687; c) H. Abdelkafi, B. Nay, *Nat. Prod. Rep.* **2012**, *29*, 845–869.

[30] M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, L. D. Jones, *J. Am. Chem. Soc.* **1975**, *97*, 2507–2516.

[31] For a recent example, see: M. G. Goncalves-Martin, S. Sigmantas, P. Renaud, *Helv. Chim. Acta* **2012**, *95*, 2502–2514, and references cited therein.

[32] α-Hydroxyindolizidines and pyrroloazepines have been synthesized by decarbonylation/oxidation of hexahydroindolizin-3-ones, see: a) M. J. Martín-López, F. Bermejo-González, *Tetrahedron Lett.* **1994**, *35*, 8843–8846; for reductive cyclization of *N*-iodoallyl imides with samarium diiodide, see: b) D.-C. Cha, C.-S. Yun, E. Yu, *Tetrahedron Lett.* **1996**, *37*, 2577–2580; c) D.-C. Cha, C.-S. Yun, Y. Lee, *J. Org. Chem.* **2000**, *65*, 621–623; titanium-mediated cyclization of ω-vinyl tethered imides: d) J. Lee, J. D. Ha, J. K. Cha, *J. Am. Chem. Soc.* **1997**, *119*, 8127–8128; e) L. Ollero, G. Mentink, F. P. J. T. Rutjies, W. N. Speckamp, H. Hiemstra, *Org. Lett.* **1999**, *1*, 1331–1334; f) S.-H. Kim, S.-I. Kim, S. Lai, J. K. Cha, *J. Org. Chem.* **1999**, *64*, 6771–6775; g) S. Santra, N. Masalov, O. L. Epstein, J. K. Cha, *Org. Lett.* **2005**, *7*, 5901–5904; hydrazinolysis of *N*-(1,3-dioxoindanyl) ethyl-substituted imides: h) C. J. Roxburgh, L. Banting, *Aust. J. Chem.* **2006**, *59*, 59–74; silylative Dieckmann-like cyclizations of ester-imides: i) R. M. de Figuereido, R. Frölich, M. Christmann, *Angew. Chem.* **2007**, *119*, 2941; *Angew. Chem. Int. Ed.* **2007**, *46*, 2883–2886; see also ref.[14] For radical cyclization of *N*-substituted cyclic imides, see: j) T. Bootwicha, D. Panichakul, C. Kuhakarn, S. Prabpai, P. Kongsaeree, P. Tuchinda, V. Reutrakul, M. Pohmakotr, *J. Org. Chem.* **2009**, *74*, 3798–3805; k) for electroreductive intramolecular coupling of imides with α,β-unsaturated esters, see: l) N. Kise, S. Isemoto, T. Sakurai, *Org. Lett.* **2009**, *11*, 4902–4905; and with ketones and *O*-methyloximes: m) N. Kise, K. Fukuzawa, T. Sakurai, *Tetrahedron Lett.* **2010**, *51*, 5767–5770; for the benzo-fused systems, see, Parham cyclization; for a recent review, see ref.[8j] Photocyclization of *N*-iodoalkyl-substituted imides: n) A. G. Griesbeck, A. Henz, K. Peters, E.-V. Peters, H. G. von Schnering, *Angew. Chem.* **1995**, *107*, 498; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 474–476; for photocyclization of *N*-silylalkyl-substituted imides, see: o) U. C. Yoon, S. W. Oh, S. M. Lee, S. J. Cho, J. Gamlin, P. S. Mariano, *J. Org. Chem.* **1999**, *64*, 4411–4418.

[33] W. C. Still, H. Kann, A. J. Miltra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[34] a) D. D. Perrin, W. L. F Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, UK, 4th ed., **1997**; b) B. G. Williams, M. Lawton, *J. Org. Chem.* **2010**, *75*, 8351–8354.

[35] P. Y. Reddy, S. Kondo, T. Toru, Y. Ueno, *J. Org. Chem.* **1997**, *62*, 2652–2664.

[36] K. L. Burgess, N. J. Lajkiewicz, A. Sanyal, W. Yan, J. K. Snyder, *Org. Lett.* **2005**, *7*, 31–34.

[37] B. P. Wijnberg, W. N. Speckamp, A. R. C. Ooestveen, *Tetrahedron* **1982**, *38*, 209–217.

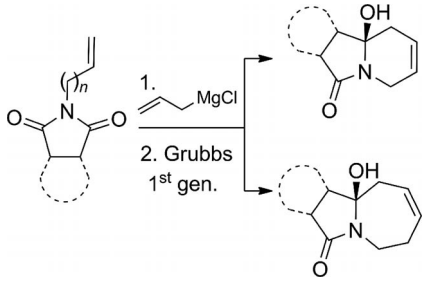
[38] K. D. Camm, N. Martinez Castro, Y. Liu, P. Czechura, J. L. Snelgrove, D. E. Fogg, *J. Am. Chem. Soc.* **2007**, *129*, 4168–4169.

[39] This compound has been reported in ref.[19a], but no spectroscopic or other characterization data were given.

Received: June 17, 2013

RCM Reactions

The sequence of allylmagnesium chloride addition/RCM sequence using *N*-alkenyl-substituted imides provides mild access to indolizinone and pyrrolozepinone derivatives with an α-hydroxy-γ-lactam framework.



Keywords: Nitrogen heterocycles / Lactams / Ring-closing metathesis / Diastereoselectivity / Grignard reaction / α-Amidoalkylation

