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Pd–Cu Bimetallic Catalyzed Domino Cyclization of α-Allenols Followed by a Coupling Reaction: New Sequence Leading to Functionalized Spirolactams

Benito Alcaide,*[a] Pedro Almendros,*[b] and Raquel Rodríguez-Acebes[a]

Dedicated to Professor Joaquín Plumet on the occasion of his 60th birthday

Abstract: A novel regioselective metal-catalyzed spirocyclization of α-allenols–cross coupling (Heck, Sonogashira, and Suzuki) reaction sequence, leading to potentially bioactive spirocyclic lactam derivatives has been developed. Precursors for the tandem spirocyclization–coupling reaction, α-allenols **2a–d** were obtained starting from α-oxolactams **1a–c** via indium-mediated Barbier-type carbonyl-allenylation reaction in aqueous media by using our previously described methodologies.

Keywords: allenes · domino reactions · lactams · palladium · spiro compounds

Introduction

The evolution of organic synthesis relies on the design and discovery of new reactions that generate structural complexity and value with step economy.[1] Towards this end, transition-metal-catalyzed processes have become a powerful tool for the construction of sensitive functionalized molecules under very mild conditions.[2] Allenes are versatile building blocks in metal-catalyzed processes but are still under utilized in organic synthesis. In the context of heterocyclic synthesis, allenes offer expeditious routes to a wide range of oxygen and nitrogen heterocycles.[3] A further feature of incorporation of allenes into heterocyclic synthesis is their ability to provide unusual substituents and substitution patterns. Metal-catalyzed domino heterocyclization–functionalization reaction of allenes are relatively unknown; only Trost and Lu have independently reported the tandem cyclization–Michael addition reaction of unsubstituted at the allene carbon atom, where the cyclization occurs, δ- and γ-allenols,[4] δ- and γ-allenamines,[5] α-allene carbamates,[6] or α-allenoic acids.[7] We are currently involved in a project aimed at the synthesis of nitrogen heterocycles.[8] We report here a novel one-pot catalyzed heterocyclization of substituted at the allene carbon α-allenols-coupling (Heck, Sonogashira, and Suzuki) reactions, leading to potentially bioactive spirolactams.[9]

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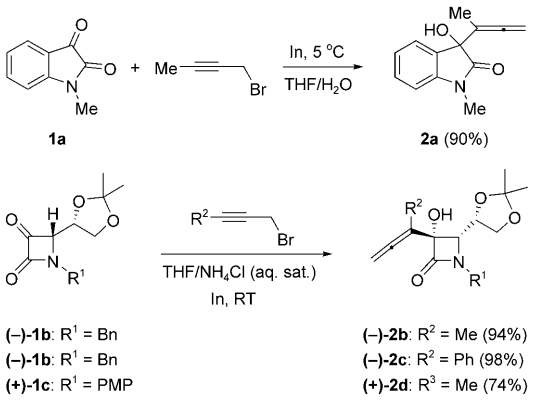
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the authors. Supporting Information: It contains compound characterization data and experimental procedures for compounds **2a–d**, **7a**, and **10**.

Results and Discussion

Precursors for the tandem spirocyclization–coupling reaction, α-allenols **2a–d** were obtained starting from α-oxolactams **1a–c** via indium-mediated Barbier-type carbonyl-allenylation reaction in aqueous media by using our previously described methodologies (Scheme 1).[10]

The final goal of this study was to intercept the halovinyl moiety of a proposed dihydrofuran intermediate with a convenient coupling partner using a multitasking catalytic system.[11] After considerable experimentation, it was found that reaction of α-allenol **2a** with methyl acrylate at room temperature in acetonitrile in the presence of 9 mol% $Pd(OAc)_2$, 0.2 equiv PPh_3, 5 equiv LiBr, 2 equiv $Cu(OAc)_2$ and 7 equiv K_2CO_3 under an atmospheric pressure of oxygen af-



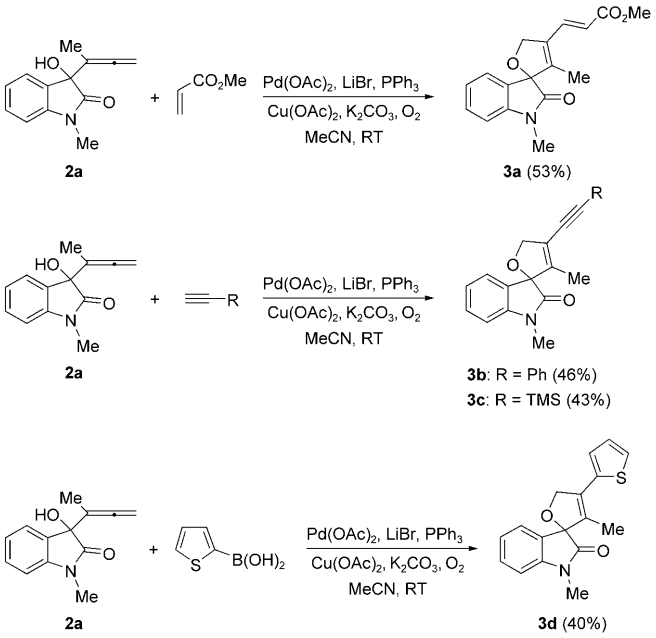
Scheme 1. Regioselective preparation of α-allenic alcohols **2** in aqueous media. PMP = 4-$MeOC_6H_4$.

forded the allene cyclization Heck trapping product **3a** in a reasonable 53% isolated yield. The use of lithium iodide instead of lithium bromide in the domino sequence gave essentially the same yield of **3a**. Compound **3a** can be considered as a hybrid scaffold as combination at the spiro junction of the oxindole and the dihydrofuran moieties.[12] When phenylacetylene, (trimethylsilyl)acetylene, or thiophene-2-boronic acid were used as the cross-coupling reagent under our optimized conditions, the corresponding domino Sonogashira or Suzuki–Miyaura adducts **3b–d** were obtained (Scheme 2). Thus, the same catalytic system is able to promote two different, but sequential catalytic cycles, allowing different transformations in a single reaction flask.

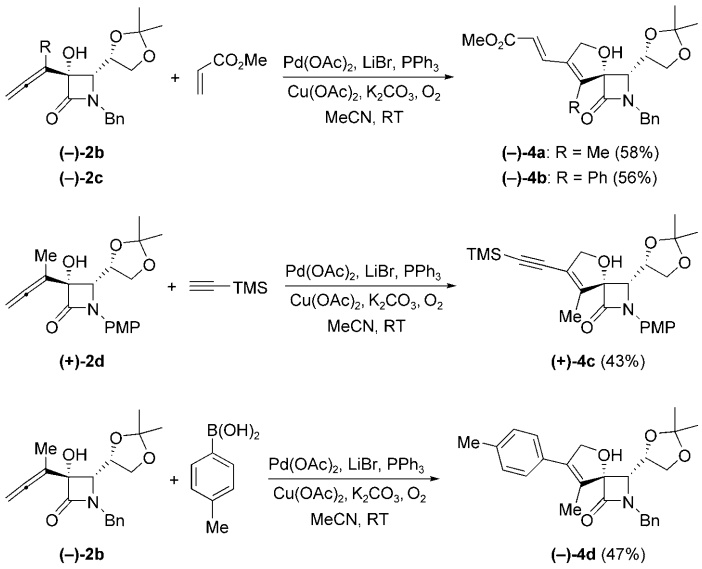
Having demonstrated that oxindole-tethered allenols were viable substrates for the domino spirocyclization–coupling process, we investigated the achievement of this single-pot catalytic sequence for the synthesis of spiranic β-lactams. Treatment of enantiopure α-allenols **2b–d** with the appropriate coupling partner under similar above conditions for allene **2a**, led to formation of the desired products **4** as single isomers (Scheme 3).

The domino cyclization reaction is highly regioselective,[13] giving five-membered heterocycles. Besides, the stereochemical integrity of the stereogenic centers at the lactam substituents, when applicable, remained unaltered.

The formation of spirolactams **3** and **4** could be rationalized in terms of a novel sequence domino cyclization of α-allenols-cross coupling reactions. A palladium(II)-catalyzed mechanism for the domino sequence leading to spiranic adducts **3** and **4** is proposed in Scheme 4.[14] It can be assumed that the initially formed allenepalladium complex **5** under-



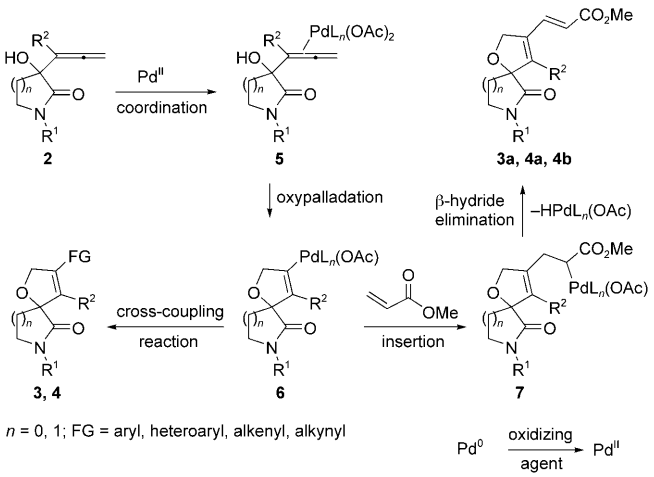
Scheme 2. One-pot synthesis of spirocyclic oxindoles **3** through metal-catalyzed domino cyclization of α-allenols-cross coupling (Heck, Sonogashira, and Suzuki) reactions. TMS = trimethylsilyl.



Scheme 3. One-pot synthesis of enantiopure spirocyclic 2-azetidinones **4** through metal-catalyzed domino cyclization of α-allenols-cross coupling (Heck, Sonogashira, and Suzuki) reactions.

Abstract in Spanish: *Se ha descubierto un nuevo proceso de espirociclación de α-alenoles-reacción de acoplamiento cruzado (Heck, Sonogashira, y Suzuki), catalizado por un sistema bimetálico Pd–Cu, que proporciona de forma totalmente regioselectiva lactamas espirocíclicas potencialmente bioactivas.*

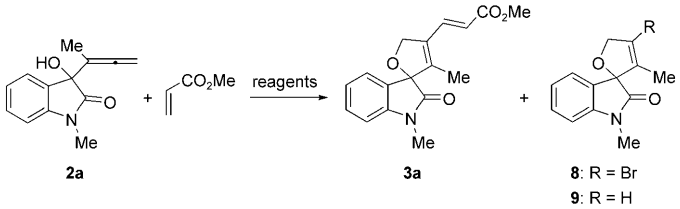
goes an intramolecular attack by the hydroxyl group (oxypalladation), giving rise to the spirocyclic vinylic palladium species **6**. Next, palladadihydrofuran intermediate **6** is trapped by the cross-coupling reagents leading to compounds **3** and **4**. For example, the palladium species **6** can then form the intermediate **7** in a subsequent Heck reaction with acrylate, which leads to the final spirocycles **3a**, **4a**, and **4b** and Pd^0 in a β-hydride elimination. It is necessary for the catalyt-



Scheme 4. Rationalization for the metal-catalyzed domino allene cyclization–coupling sequence.

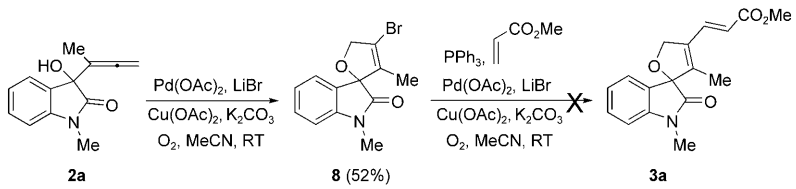
ic cycle that Pd^0 is reoxidized to Pd^{II}; this is achieved by the addition of $Cu(OAc)_2$, which does not interfere with the course of the reaction.

To gain an insight into the mechanism, additional experiments were carried out (Schemes 5, 6, Table 1). When the sequence was conducted step by step, it was possible to isolate the bromodihydrofuran **8**, which after addition of methyl acrylate and PPh_3 to the catalytic medium did not afforded spirolactam **3a** (Scheme 5).[15] In the absence of lithium bromide, the spirocyclization tandem reaction occurred as well, but led to a significantly decreased yield of **3a** (24%) (Table 1, entry 1). The use of lithium fluoride instead of lithium bromide in the domino sequence under the same conditions resulted in a considerable lower yield (Table 1, entry 2). Replacing $Pd(OAc)_2$ with $PdCl_2$ in the domino sequence gave rise to a complex mixture; bromodihydrofuran **8** was obtained as the major component (Table 1, entry 3). The absence of $Cu(OAc)_2$ and oxygen (Table 1, entry 4), or the absence of LiBr, $Cu(OAc)_2$ and oxygen (Table 1, entry 5) on the standard reaction conditions afforded mixtures of the domino adduct **3a** and the dihydrofuran **9** albeit in modest yields.



Scheme 6. Reaction of α-allenol **2a** under modified domino cyclization conditions.

Although the exact mechanism of this tandem allene heterocyclization reaction has yet to be elucidated, it is obvious that the presence of the bromide ion is not essential. However, it plays an important role on increasing the yield of the final domino adduct.[16] The bromodihydrofuran derivative **8** was not an intermediate in the formation of the domino adduct **3a**, since it was not converted into **3a** under the reaction conditions. This result rules out the possibility that oxybromination occurs first, followed by the cross-coupling reaction. At the present time, based on the experimental evidences of Schemes 5, 6, and Table 1, we propose the mechanism outlined in Scheme 4.[14]



Scheme 5. Metal-catalyzed oxybromination of the α-allenol **2a** followed by the addition of the cross-coupling reagent.

Table 1. Reaction of α-allenol **2a** under modified domino cyclization conditions.[a]

	Reagents[a]	Product [yield (%)][b]
1	$Pd(OAc)_2$, PPh_3, $Cu(OAc)_2$, K_2CO_3, O_2	**3a** [24]
2	$Pd(OAc)_2$, LiF, PPh_3, $Cu(OAc)_2$, K_2CO_3, O_2	**3a** [18]
3	$PdCl_2$, LiBr, PPh_3, $Cu(OAc)_2$, K_2CO_3, O_2	**8** [8]
4	$Pd(OAc)_2$, LiBr, PPh_3, K_2CO_3	**3a** [16], **9** [8]
5	$Pd(OAc)_2$, PPh_3, K_2CO_3	**3a** [10], **9** [11]

[a] All reactions were conducted in dry acetonitrile at room temperature. [b] Yield of pure, isolated product with correct analytical and spectral data. Disappearance of starting **2a** was observed in all cases. Unidentified decomposition products were also detected.

Conclusion

In summary, using a single catalytic system we have successfully accomplished an unprecedented domino cyclization of α-allenols-cross coupling reaction strategy for the synthesis of potentially bioactive spirolactams.

Experimental Section

General methods: Melting points were obtained with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 781 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low and high resolution mass spectra were taken

on a HP5989A spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Specific rotation $[\alpha]_D$ is given in deg cm^2 g^{-1} at 25 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification. THF was distilled from Na/benzophenone. Benzene, dichloromethane and triethylamine were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh).

Metal-catalyzed domino cyclization of α-allenols–cross coupling reactions—General procedure for the synthesis of spirolactams 3a–d and 4a–d: Palladium(II) acetate (0.009 mmol), triphenylphosphine (0.02 mmol), lithium bromide (0.49 mmol), potassium carbonate (0.70 mmol), copper(II) acetate (0.21 mmol), and the appropriate coupling reagent (0.12 mmol) were sequentially added to a stirred solution of the corresponding α-allenic alcohol **2** (0.10 mmol) in acetonitrile (5 mL). The resulting suspension was stirred at room temperature under an oxygen atmosphere until disappearance (TLC) of the starting material. The organic phase was diluted with brine (2 mL), extracted with ethyl acetate (5× 5 mL), washed with brine (2 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure spirolactams **3** and **4**. Spectroscopic and analytical data for some representative pure forms follow.[17]

Spirolactam 3a: From α-allenol **2a** (36 mg, 0.167 mmol), compound **3a** was obtained as a colorless solid (27 mg, 53 %). M.p. 128–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.54 (d, J = 15.9 Hz, 1H), 7.36 (td, J = 7.6, 1.6 Hz, 1H), 7.17 (ddd, J = 7.3, 1.7, 0.5 Hz, 1H), 7.08 (td, J = 7.3, 1.0 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 5.79 (d, J = 15.9 Hz, 1H), 5.19, 5.07 (ddd, J = 11.1, 1.7, 0.7 Hz, 1H each), 3.80 (s, 3H), 3.21 (s, 3H), 1.58 (t, J = 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 174.8, 167.0, 144.0, 141.2, 133.8, 133.0, 130.5, 127.7, 124.6, 123.4, 120.1, 108.5, 94.3, 75.8, 51.7, 26.4, 9.8; IR ($CHCl_3$): $\tilde{\nu}$ = 1720, 1716 cm^{-1}; MS (EI): m/z (%): 299 (100) $[M]^+$, 284 (90) $[M-CH_3]^+$; elemental analysis calcd (%) for $C_{17}H_{17}NO_4$ (299.3): C 68.21, H 5.72, N 4.68; found C 68.33, H 5.75, N 4.65.

Spirolactam 3b: From α-allenol **2a** (45 mg, 0.209 mmol), compound **3b** was obtained as a colorless oil (30 mg, 46 %). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.60 (m, 1H), 7.31 (m, 6H), 7.12 (dd, J = 7.3, 1.0 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 5.60 (t, J = 1.0 Hz, 2H), 3.23 (s, 3H), 1.49 (t, J = 2.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 175.4, 144.0, 140.8, 137.2, 133.6, 130.3, 128.9, 128.4, 127.7, 124.7, 123.3, 122.2, 108.4, 94.0, 77.1, 76.7, 75.8, 26.4, 10.2; IR ($CHCl_3$): $\tilde{\nu}$ = 1714 cm^{-1}; MS (ES): m/z (%): 316 (100) $[M+H]^+$, 315 (61) $[M]^+$; elemental analysis calcd (%) for $C_{21}H_{17}NO_2$ (315.4): C 79.98, H 5.43, N 4.44; found C 79.84, H 5.40, N 4.46.

Spirolactam 3c: From α-allenol **2a** (36 mg, 0.167 mmol), compound **3c** was obtained as a colorless oil (22 mg, 43 %). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.31 (m, 2H), 7.08 (m, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.54 (d, J = 1.5 Hz, 2H), 3.21 (s, 3H), 1.43 (t, J = 1.8 Hz, 3H), 0.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.9, 144.0, 134.3, 132.6, 130.3, 128.3, 124.7, 123.3, 108.4, 93.5, 77.2, 75.8, 74.7, 26.4, 10.1, −1.9; IR ($CHCl_3$): $\tilde{\nu}$ = 1710 cm^{-1}; MS (ES): m/z (%): 312 (100) $[M+H]^+$, 311 (10) $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{21}NO_2Si$ (311.5): C 69.41, H 6.80, N 4.50; found C 69.55, H 6.76, N 4.53.

Spirolactam 3d: From α-allenol **2a** (27 mg, 0.126 mmol), compound **3d** was obtained as a colorless oil (14 mg, 40 %). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 3H), 7.09 (m, 2H), 7.03 (td, J = 3.7, 1.0 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 5.40, 5.28 (dq, J = 11.0, 2.0 Hz, 1H each), 3.23 (s, 3H), 1.67 (t, J = 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.7, 146.8, 144.2, 134.9, 130.3, 129.6, 128.3, 127.0, 125.7, 124.8, 123.3, 108.4, 87.4, 78.1, 26.4, 10.9; IR ($CHCl_3$): $\tilde{\nu}$ = 1711 cm^{-1}; MS (ES): m/z (%): 298 (100) $[M+H]^+$, 297 (16) $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{15}NO_2S$ (297.4): C 68.66, H 5.08, N 4.71; found C 68.80, H 5.11, N 4.68.

Spirolactam (−)-4a: From α-allenol (−)-**2b** (32 mg, 0.098 mmol), and after chromatography of the residue using hexanes/ethyl acetate 3:1 gave compound (−)-**4a** (23 mg, 58 %) as a colorless oil. $[\alpha]_D$ = −79.7 (c = 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40 (d, J = 16.1 Hz, 1H), 7.35 (m, 5H), 5.65 (d, J = 16.1 Hz, 1H), 4.91 (d, J = 14.4 Hz, 1H), 4.40 (m, 1H), 4.21 (d, J = 14.4 Hz, 1H), 4.11 (dd, J = 10.4, 6.9 Hz, 1H), 3.77 (s, 3H), 3.75 (m, 1H), 3.44 (t, J = 8.9 Hz, 1H), 3.39 (dd, J = 8.7, 5.5 Hz, 1H), 1.70 (t, 3H, J = 1.8 Hz), 1.40, 1.35 (s, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.5, 167.2, 135.9, 133.4, 132.6, 129.5, 129.1, 128.4, 120.9, 110.3, 102.3, 77.6, 76.1, 66.8, 64.2, 52.3, 45.8, 27.1, 25.3, 9.8; IR ($CHCl_3$): $\tilde{\nu}$ = 1748, 1718 cm^{-1}; MS (ES): m/z (%): 414 (100) $[M+H]^+$, 413 (25) $[M]^+$; elemental analysis calcd (%) for $C_{23}H_{27}NO_6$ (413.5): C 66.81, H 6.58, N 3.39; found C 66.93, H 6.55, N 3.37.

Spirolactam (−)-4b: From α-allenol (−)-**2c** (50 mg, 0.128 mmol), compound (−)-**4b** was obtained as a colorless oil (56 %, 34 mg). $[\alpha]_D$ = −4.6 (c = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.25 (m, 9H), 6.82 (dd, J = 7.7, 1.4 Hz, 1H), 5.75 (d, J = 16.1 Hz, 1H), 5.10 and 4.88 (d, J = 12.0 Hz, 1H), 4.79 (d, J = 14.4 Hz, 1H), 4.41 (ddd, J = 8.9, 6.7, 5.9 Hz, 1H), 4.13 (m, 1H), 4.12 (d, J = 14.6 Hz, 1H), 3.72 (s, 3H), 3.43 (dd, J = 8.4, 5.5 Hz, 1H), 3.28 (d, J = 8.8 Hz, 1H), 1.30 and 1.19 (s, each 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.1, 166.5, 142.1, 135.0, 134.6, 133.9, 130.0, 129.2, 129.1, 129.0, 128.4, 128.3, 127.3, 122.1, 109.9, 102.2, 76.8, 75.7, 66.5, 64.1, 51.8, 45.1, 26.4, 24.8.; IR ($CHCl_3$): $\tilde{\nu}$ = 1750, 1716 cm^{-1}; MS (ES): m/z (%): 476 (100) $[M+H]^+$, 475 (30) $[M]^+$; elemental analysis calcd (%) for $C_{28}H_{29}NO_6$ (475.5): C 70.72, H 6.15, N 2.95; found C 70.58, H 6.20, N 2.98.

Spirolactam (+)-4c: From α-allenol (+)-**2d** (34 mg, 0.10 mmol), compound (+)-**4c** was obtained as a colorless oil (19 mg, 43 %). $[\alpha]_D$ = +5.8 (c = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.73, 6.89 (d, J = 9.0 Hz, 2H each), 5.36, 5.20 (dqd, J = 12.5, 2.0, 1.0 Hz, 1H), 4.48 (m, 1H), 4.29 (dd, J = 8.5, 7.1 Hz, 1H), 4.10 (d, J = 8.5 Hz, 1H), 3.81 (s, 3H), 3.58 (dd, J = 8.7, 6.2 Hz, 1H), 1.75 (t, 3H, J = 2.1 Hz), 1.63, 1.35 (s, 3H each), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 167.6, 156.7, 133.2, 130.9, 129.3, 119.8, 114.1, 109.9, 103.3, 77.4, 77.2, 75.6, 74.5, 68.9, 66.7, 55.5, 26.7, 24.7, 9.8, 1.0; IR ($CHCl_3$): $\tilde{\nu}$ = 1746 cm^{-1}; MS (ES): m/z (%): 442 (100) $[M+H]^+$, 441 (15) $[M]^+$; elemental analysis calcd (%) for $C_{24}H_{31}NO_5Si$ (441.6): C 65.28, H 7.08, N 3.17; found C 65.39, H 7.05, N 3.15.

Spirolactam (−)-4d: From α-allenol (−)-**2b** (33 mg, 0.10 mmol), compound (−)-**4d** was obtained as a colorless oil (20 mg, 47 %). $[\alpha]_D$ = −92.5 (c = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 5H), 7.15 (m, 4H), 5.09 (dq, J = 12.2, 2.0 Hz, 1H), 4.94 (d, J = 14.2 Hz, 1H), 4.83 (dq, J = 12.2, 2.0 Hz, 1H), 4.44 (ddd, J = 8.9, 6.8, 5.4 Hz, 1H), 4.23 (d, J = 14.2 Hz, 1H), 4.15 (dd, J = 8.7, 7.0 Hz, 1H), 3.50 (dd, J = 8.5, 5.6 Hz, 1H), 3.49 (d, J = 9.0 Hz, 1H), 2.35 (s, 3H), 1.66 (t, 3H, J = 2.0 Hz), 1.41, 1.36 (s, 3H each); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.2, 138.0, 135.8, 135.1, 129.5, 129.3, 129.1, 128.5, 127.8, 127.4, 125.8, 109.8, 102.9, 78.3, 77.5, 66.5, 64.2, 45.3, 26.7, 24.9, 21.2, 9.9; IR ($CHCl_3$): $\tilde{\nu}$ = 1751 cm^{-1}; MS (ES): m/z (%): 420 (100) $[M+H]^+$, 419 (22) $[M]^+$; elemental analysis calcd (%) for $C_{26}H_{29}NO_4$ (419.5): C 74.44, H 6.97, N 3.34; found C 74.58, H 6.94, N 3.32.

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[17] Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

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