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# Synthesis of a Leucomitosane via a Diastereoselective Radical Cascade

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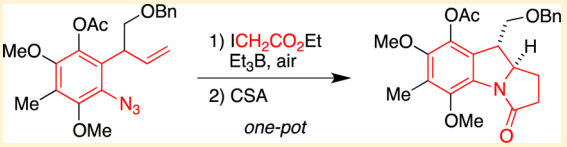
Supporting Information

**ABSTRACT:** The preparation of *trans*-2,3-disubstituted indolines from 1-azido-2-allylbenzene derivatives via a diastereoselective radical cascade using ethyl iodoacetate and triethylborane is described. Further lactamization afforded substituted benzopyrrolizidinones with excellent diastereomeric ratios. The radical cascade/lactamization sequence was efficiently applied to the synthesis of a 3-oxo-leucomitosane related to the mitomycin family of alkaloids.

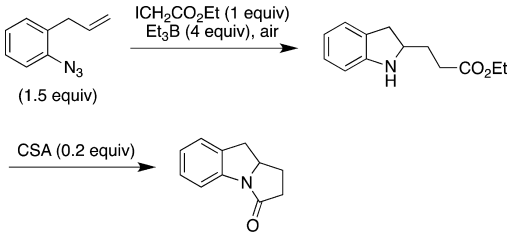



## INTRODUCTION

The indoline skeleton is present in a vast class of natural products possessing diverse biological activities.[1] The development of efficient methods to prepare and functionalize this scaffold has been a major area of interest for synthetic organic chemists, and new strategies allowing for the rapid construction of functionalized indolines are still highly demanded.[2] Over the past several years, the development of processes involving the formation of carbon−nitrogen bonds via radical addition on a nitrogen atom of a suitable trap has become a field of intense research.[3] Toward this goal, organic azides have proven to be among the most attractive radical traps.[4,5] Kim and co-workers took advantage of this reactivity to prepare aliphatic N-heterocycles by radical cyclizations onto alkyl azides.[6] A related strategy was applied by Murphy and co-workers to the synthesis of aspidospermidine and vindoline.[7,8] Recently, we reported a mild and efficient procedure to prepare indolines and benzopyrrolizidinones via a tandem radical addition/cyclization on *ortho*-azidoallylbenzenes using ethyl iodoacetate and $Et_3B$ to initiate and sustain the process (Scheme 1).[9]

The benzopyrrolizidine ring system constitutes the core structure of the mitomycins, an important family of alkaloids (Figure 1). These natural quinone products have attracted the attention from the scientific community during the last fifty years because of their potent antibiotic and antitumor properties,[10] as well as their highly challenging molecular architecture.[11,12] The related hydroquinones, protected or not, and lacking both the oxygenate residue at C(9a) and the aziridine ring, are named leucomitosanes and have been considered as intermediates in the synthesis of mitomycins.[11a]

**Scheme 1. Previously Reported Indoline and Benzopyrrolizidinone Synthesis via a Radical Cascade**



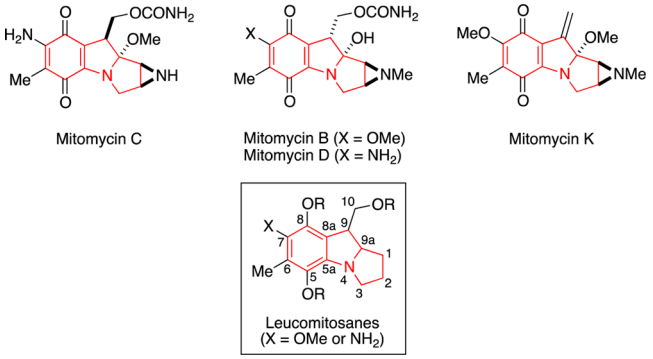




**Figure 1.** Examples of mitomycins.

So far, our radical cascade strategy has been used for the preparation of unfunctionalized and monofunctionalized model systems. Now, we report the extension of our process to the preparation of more functionalized systems, and we describe the diastereoselective synthesis of a leucomitosane.

## RESULTS AND DISCUSSION

**Stereoselective Tandem Radical Addition/Cyclization Process.** In order to study the stereoselectivity of the radical cascade reaction, simple 1-azido-2-allylbenzenes **1a−c** were prepared from commercially available compounds, according to literature procedures (Scheme 2). The methyl-substituted azide **1a** was obtained in five steps from aniline via N-alkylation, aza-Claisen rearrangement, and mild conversion into aryl azide upon treatment with *tert*-butyl nitrite and trimethylsilyl azide.[13] Azides **1b** and **1c** were also prepared in five steps, starting from

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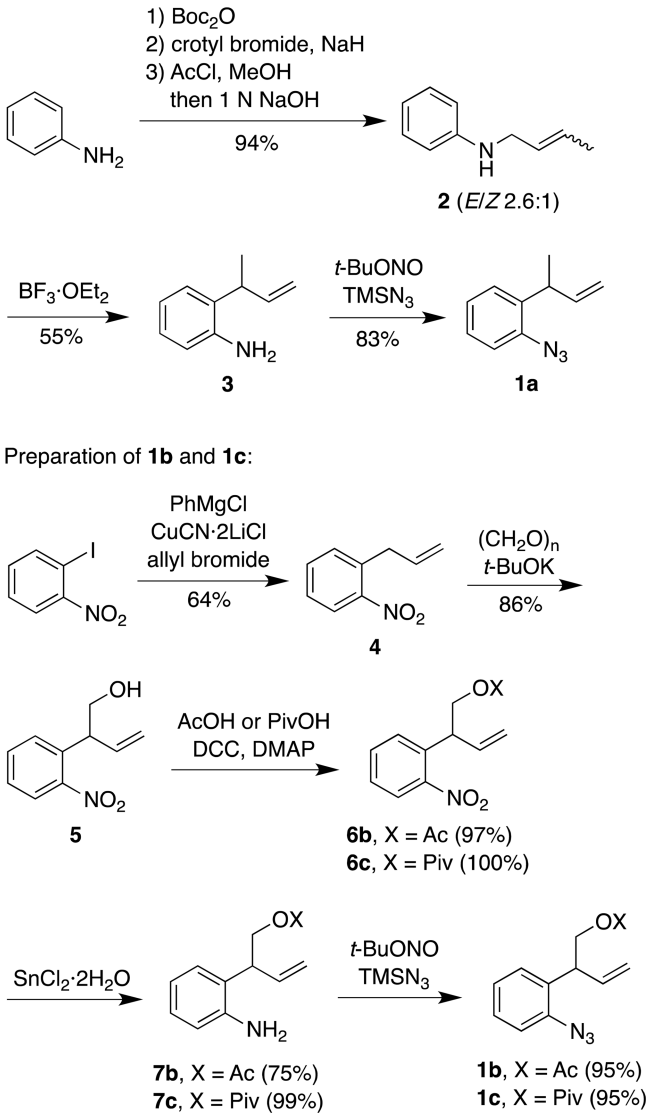
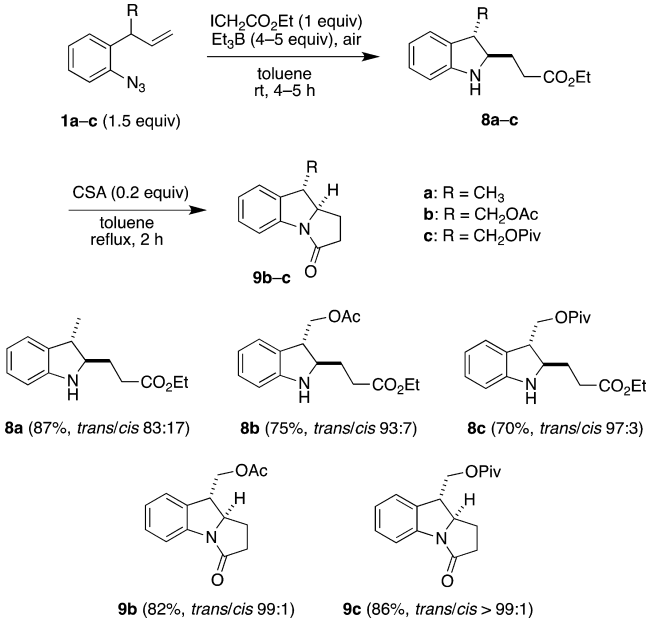
**Scheme 2. Preparation of 1-Azido-2-allylbenzenes 1a−c**




**Scheme 3. Stereoselective Synthesis of Indolines 8a−c and Benzopyrrolizidinones 9b−c from Azidoalkenes 1a−c**




1-iodo-2-nitrobenzene, via allylation using Knochel's conditions,[14] followed by hydroxymethylation,[15] transformation of the resulting primary alcohol into an acetate or a pivaloyl ester, reduction of the nitro group, and final conversion into aryl azide.

Treatment of the azides **1a−c** with ethyl iodoacetate in the presence of triethylborane, according to previously reported conditions, afforded the 2,3-disubstituted indolines **8a−c** in good to high yields (>70%) and gratifying diastereoselectivities (dr up to 97:3) (Scheme 3). The reactions were run in toluene to minimize the formation of the corresponding indoles.[9] The scale of the reactions had an influence on the yields of indolines. For instance, **8c** was obtained in 70% yield when the cascade was carried out with 0.4 mmol of **1c**, but the yield dropped to 55−60% when 2−5 mmol of **1c** was used. In the latter case, significant amounts of starting azide remained unreacted and could easily be recovered by column chromatography to be reused. In accordance with the Beckwith−Schiesser−Houk rules,[16,17] a high level of *trans* stereocontrol was obtained during the radical cyclization step. The relative *trans* configuration of the major diastereomers of indolines **8** was confirmed by NOE difference experiments on both isomers of **8a** and on the major isomers of **8b** and **8c** (see the Supporting Information). The level of diastereoselectivity of the cyclization step was influenced by the size of the benzylic side chain, with the highest diastereoselectivity being obtained for **8c** (R = $CH_2OPiv$). Treatment of indolines **8b** and **8c** with 0.2 equiv of camphorsulfonic acid (CSA) afforded the benzopyrrolizidinones **9b** and **9c**, respectively, in high yields and as single diastereomers (*trans*/*cis* ≥ 99:1) after purification by flash column chromatography.

**Synthesis of a 3-Oxo-leucomitosane.** By designing a suitable 1-azido-2-allylbenzene intermediate, our radical cascade was expected to allow for the preparation of a leucomitosane. In order to test the viability of our approach, the highly functionalized 1-azido-2-allylbenzene **17** was prepared from 2,6-dimethoxytoluene (Scheme 4). Following the strategy developed by Danishefsky and co-workers for the preparation of functionalized anilines during the synthesis of mitosanes,[18,19] the aniline **16** was first constructed and then conveniently transformed into the aryl azide **17**. With this optimized 10-step sequence, a total amount of 670 mg of **17** was prepared in 20% overall yield from commercially available materials. The azide **17** was immediately used in the next step after purification. Indeed, partial decomposition of **17** was observed at room temperature within a few hours, presumably by intramolecular dipolar cycloaddition.

Treatment of **17** with ethyl iodoacetate and $Et_3B$ afforded the 2,3-disubstituted indoline **18** in 80% yield and as a 97:3 *trans*/*cis* mixture of diastereomers (Scheme 5). The leucomitosane derivative **19** was subsequently obtained in 87% yield (*trans*/*cis* 97:3) from **18** upon heating in toluene and in the presence of CSA. The radical cascade/lactamization sequence could also be achieved by a one-pot process and furnished **19** in 80% yield from **17** as a similar 97:3 *trans*/*cis* mixture.

## ■ CONCLUSION

The tandem radical addition/cyclization procedure on a 1-azido-2-allylbenzene intermediate, polysubstituted on the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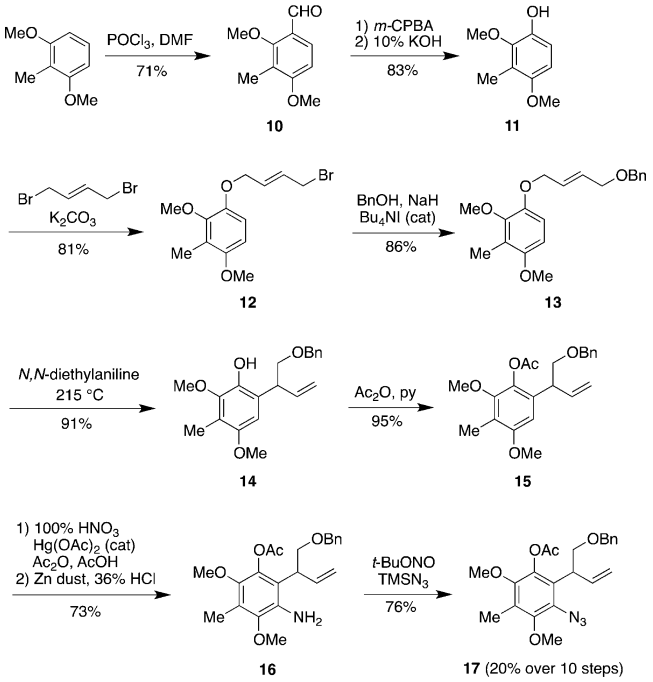
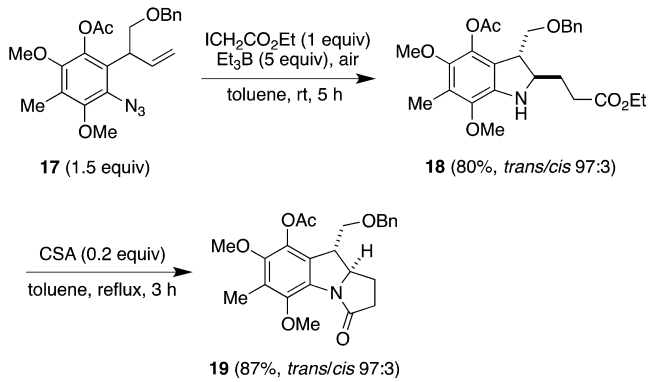
**Scheme 4. Preparation of the 1-Azido-2-allylbenzene 17**

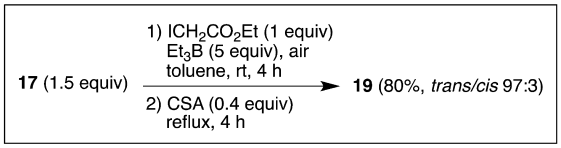



**Scheme 5. Diastereoselective Synthesis of the 3-Oxo-leucomitosane 19**

Stepwise synthesis of **19**:




One-pot synthesis of **19**:




aromatic ring and possessing a benzylic side chain, was found to be suitable for the efficient preparation of a leucomitosane. A high level of stereocontrol was obtained during the cyclization step, allowing for the diastereoselective synthesis of the *trans*-leucomitosane. Interestingly, the presence of a polysubstituted electron-rich aromatic ring did not interfere with the radical process. Based on these results, an approach for the rapid synthesis of the naturally occurring mitomycins is currently under investigation.

## EXPERIMENTAL SECTION

**General Methods.** All reactions requiring anhydrous conditions were performed in heat-gun dried glassware under an argon atmosphere. Silica gel 60 (230−400 mesh) was used for flash column chromatography. Thin layer chromatography was performed on silica gel 60 $F_{254}$ plates with visualization under UV light (254 nm) or by submerging in a solution of ceric ammonium molybdate with subsequent heating. Commercial reagents were used as received, unless otherwise stated. Solvents for reactions (distilled THF, $CH_3CN$, $CH_2Cl_2$, and toluene) were filtered over columns of dried alumina under a positive pressure of argon. Solvent for extractions and flash column chromatography were of technical grade and distilled prior to use. $^1H$ and $^{13}C$ NMR spectra were recorded using a spectrometer operating at 300 or 400 MHz for $^1H$ and 75 or 100 MHz for $^{13}C$ at 22 °C, unless otherwise stated. Chemical shifts ($\delta$) are reported in parts per million (ppm) using the residual solvent ($CHCl_3$ $\delta$ = 7.26 for $^1H$ NMR spectra and $CDCl_3$ $\delta$ = 77.0 for $^{13}C$ NMR spectra) or $Si(CH_3)_4$ ($\delta$ = 0.00 for $^1H$ NMR spectra), as an internal standard. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and br (broad). Coupling constants ($J$) are reported in Hz. Infrared spectra were recorded on a FT-IR spectrometer and are reported in wave numbers ($cm^{-1}$). Low-resolution mass spectra were recorded in EI mode at 70 eV using a quadrupole mass analyzer. High-resolution mass spectra and accurate mass determinations were performed on a mass spectrometer using ESI mode and an LTQ Orbitrap XL mass analyzer. GC analyses were carried out on a GC instrument fitted with an Optima delta-3-0.25 $\mu$m capillary column (20 m, 0.25 mm); gas carrier, He 1.4 mL/min; injector, 220 °C split mode; detector, FID 280 °C, $H_2$ 35 mL/min, air 350 mL/min. All melting points are uncorrected.

***N*-(But-2-en-1-yl)aniline (2).** To a solution of aniline (1.00 g, 10.74 mmol) in dry THF (20 mL) at rt under argon was added a solution of $Boc_2O$ (2.58 g, 11.81 mmol) in dry THF (5 mL). The reaction mixture was stirred at rt for 72 h. The solvent was evaporated under reduced pressure. The crude product obtained (2.32 g) was dissolved in dry THF (90 mL) under argon at 0 °C, and NaH (55% dispersion in oil, 1.05 g, 24.00 mmol) was added portionwise. The reaction mixture was allowed to warm up to rt for 30 min, then crotyl bromide (1:5 mixture of *cis* and *trans* isomers, 85% purity, 2.91 mL, 24.00 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and refluxed for 16 h. The reaction was cooled down to rt, $Et_2O$ (30 mL) was added, then water was carefully added dropwise (15 mL), followed by brine (15 mL). The two layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product (3.32 g) was used in the next step without further purification. Acetyl chloride (7.63 mL, 107.00 mmol) was carefully added to MeOH (35 mL) at 0 °C under argon, then a solution of the crude product (3.32 g) in MeOH (12 mL) was added dropwise. The reaction mixture was allowed to warm up to rt and was stirred for 2 h. The mixture was concentrated under reduced pressure. The residue was treated with 1 N NaOH (25 mL) at 0 °C and extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 99:1) gave **2** (1.49 g, 10.10 mmol, 94% yield from aniline, *E*/*Z* 2.6:1 as determined by $^1H$ NMR) as a yellow liquid. The isomers were not separated. Physical and spectral data were in accordance with literature data.[20] (*E*)/(*Z*)-**2**: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.21−7.13 (m, 2H major + 2H minor), 6.75−6.66 (m, 1H major + 1H minor), 6.64−6.58 (m, 2H major + 2H minor), 5.79−5.50 (m, 2H major + 2H minor), 3.79−3.74 (m, 2H minor), 3.70−3.60 (m, 3H major + 1H minor), 1.75−1.66 (m, 3H major + 3H minor). (*E*)-**2**: $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 148.27, 129.20 (2C), 128.1, 127.9, 117.4, 112.97 (2C), 46.0, 17.7. MS (EI, 70 eV) *m*/*z* (%) 147 ($M^+$, 83), 132 (100), 117 (28), 106 (53), 93 (87), 77 (33), 55 (57), 51 (26), 39 (18). (*Z*)-**2**: $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 148.34, 129.22 (2C), 127.7, 127.1, 117.5, 112.96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(2C), 40.9, 13.1; MS (EI, 70 eV) *m*/*z* (%) 147 ($M^+$, 59), 132 (77), 117 (28), 106 (59), 93 (100), 77 (26), 55 (35), 51 (23), 39 (18).

**2-(But-3-en-2-yl)aniline (3).** To a solution of **2** (1.03 g, 6.99 mmol, *E*/*Z* 2.6:1 as determined by $^1$H NMR) in xylenes (14 mL) under argon at rt was added $BF_3{\cdot}OEt_2$ (1.05 mL, 8.38 mmol) dropwise. The reaction mixture was refluxed for 18 h, then cooled to rt, and 1 N NaOH (23 mL) was added. The two layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 15:1) gave **3** (566 mg, 3.85 mmol, 55%) as a yellow liquid. Physical and spectral data were in accordance with literature data:[21] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.10 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.05 (td, *J* = 7.6, 1.2 Hz, 1H), 6.78 (td, *J* = 7.8, 1.5 Hz, 1H), 6.67 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.01−5.88 (m, 1H), 5.13−5.04 (m, 2H), 3.65 (br s, 2H), 3.53−3.42 (m, 1H), 1.40 (d, *J* = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 144.3, 142.2, 128.9, 127.15, 127.11, 119.0, 116.2, 113.8, 38.2, 18.7; MS (EI, 70 eV) *m*/*z* (%) 147 ($M^+$, 51), 132 (100), 130 (23), 117 (43), 115 (25), 103 (10), 91 (14), 77 (19), 65 (15), 51 (11), 39 (11).

**1-Azido-2-(but-3-en-2-yl)benzene (1a).** The compound was prepared according to Moses's procedure.[13] ***Cautions:*** *ortho-Azidoallylbenzene derivatives are heat-sensitive and can undergo intramolecular cycloaddition. For this reason, the evaporations were always performed under reduced pressure at 30−35 °C using a rotary evaporator. $TMSN_3$ is volatile, latex-permeable, and absorbed by the skin. $TMSN_3$ is known to be hydrolytically unstable, resulting in the release of hydrazoic acid, an unstable and very toxic compound.* To a solution of **3** (327 mg, 2.22 mmol) in dry $CH_3CN$ (5 mL) at 0 °C under argon was added *t*-BuONO (90% purity, 0.44 mL, 3.33 mmol) dropwise followed by slow addition of $TMSN_3$ (0.35 mL, 2.66 mmol). The mixture was stirred at 0 °C for 5 min, allowed to warm to rt, and stirred for 2 h. The mixture was concentrated under reduced pressure. Purification by flash column chromatography (pentane) gave **1a** (319 mg, 1.84 mmol, 83%) as a yellow liquid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.29−7.06 (m, 4H), 6.05−5.92 (m, 1H), 5.07 (d, *J* = 1.6 Hz, 1H), 5.02 (dt, *J* = 7.8, 1.6 Hz, 1H), 3.86−3.75 (m, 1H), 1.30 (d, *J* = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 142.1, 137.3, 136.9, 128.0, 127.4, 124.9, 118.2, 113.5, 36.7, 19.6; IR (neat) 3078, 2967, 2867, 2120, 2089, 1637, 1580, 1486, 1446, 1282, 997, 913, 747; MS (EI, 70 eV) *m*/*z* (%) 145 ($M^+ - N_2$, 46), 144 (75), 143 (11), 130 (100), 115 (16), 103 (27), 91 (10), 77 (29), 65 (14), 51 (19), 39 (14); HRMS (ESI) calcd for $C_{10}H_{12}N$ 146.0964, found 146.0966.

**1-Allyl-2-nitrobenzene (4).** The compound was prepared according to Knochel's procedure[14] from 1-iodo-2-nitrobenzene (4.00 g, 16.00 mmol), PhMgCl (9.80 mL, 17.60 mmol, 1.8 M in THF), CuCN·2LiCl (17.60 mL, 17.60 mmol, 1 M in THF), and allyl bromide (1.63 mL, 19.20 mmol) in dry THF (40 mL). Purification by flash column chromatography (cyclohexane/AcOEt 99:1) gave **4** (1.68 g, 10.30 mmol, 64%) as an orange liquid. Physical and spectral data were in accordance with literature data:[14] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.54 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42−7.34 (m, 2H), 6.05−5.90 (m, 1H), 5.15−5.04 (m, 2H), 3.69 (d, *J* = 6.5 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.4, 135.1, 134.8, 133.0, 131.9, 127.3, 124.6, 117.1, 36.9; MS (EI, 70 eV) *m*/*z* (%) 163 ($M^+$, 2), 162 (14), 146 (40), 134 (30), 129 (17), 115 (100), 104 (22), 91 (73), 77 (54), 65 (34), 51 (33).

**2-(2-Nitrophenyl)but-3-en-1-ol (5).** The compound was prepared according to Steiner's procedure.[15] To a solution of **4** (3.00 g, 18.40 mmol) in dry DMSO (15 mL) under argon at rt was added paraformaldehyde (828 mg, 27.60 mmol) followed by *t*-BuOK (82 mg, 0.73 mmol). The mixture was stirred at rt for 18 h. Brine (20 mL) and AcOEt (20 mL) were added, the two layers were separated, and the aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), then water (2 × 10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 4:1) gave **5** (3.05 g, 15.80 mmol, 86%) as an orange oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.80 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.62−7.53 (m, 1H), 7.49 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.38 (td, *J* = 8.2, 1.6 Hz, 1H), 6.00 (ddd, *J* = 17.3, 10.4, 6.8 Hz, 1H), 5.27 (dt, *J* = 10.4, 1.3 Hz, 1H), 5.20 (dt, *J* = 17.3, 1.3 Hz, 1H), 4.18 (q, *J* = 6.8 Hz, 1H), 4.00−3.84 (m, 2H), 1.73−1.67 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.5, 136.5, 135.2, 132.6, 129.5, 127.5, 124.4, 118.2, 65.5, 45.9; IR (neat) 3392 (br), 2946, 2878, 1519, 1481, 1418, 1349, 1045, 993, 922, 853, 782, 745, 710; MS (EI, 70 eV) *m*/*z* (%) 193 ($M^+$, 0.1), 174 (4), 163 (10), 162 (14), 146 (61), 134 (52), 117 (43), 116 (59), 115 (100), 104 (25), 91 (56), 77 (57), 65 (36), 55 (35), 39 (32); HRMS (ESI) calcd for $C_{10}H_{12}NO_3$ 194.0812, found 194.0817.

**2-(2-Nitrophenyl)but-3-en-1-yl acetate (6b).** A solution of acetic acid (0.23 mL, 4.04 mmol) in dry $CH_2Cl_2$ (8 mL) was added to a solution of DCC (897 mg, 4.35 mmol) and DMAP (76 mg, 0.62 mmol) in dry $CH_2Cl_2$ (52 mL) at rt under argon. After 15 min, a solution of **5** (600 mg, 3.10 mmol) in dry $CH_2Cl_2$ (16 mL) was added dropwise. The reaction mixture was stirred at rt for 6 h and then filtered through a pad of Celite (rinsed with $CH_2Cl_2$). The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 8:1) gave **6b** (707 mg, 3.00 mmol, 97%) as a yellowish liquid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.80 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.61−7.54 (m, 1H), 7.45 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.40 (ddd, *J* = 8.1, 7.3, 1.5 Hz, 1H), 5.99 (ddd, *J* = 17.2, 10.5, 6.3 Hz, 1H), 5.25 (dt, *J* = 10.5, 1.1 Hz, 1H), 5.21−5.13 (m, 1H), 4.46 (dd, *J* = 9.7, 6.0 Hz, 1H), 4.42−4.35 (m, 1H), 4.28 (dd, *J* = 9.7, 6.8 Hz, 1H), 1.99 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.7, 150.4, 135.7, 134.6, 132.6, 129.5, 127.8, 124.4, 118.0, 66.0, 42.2, 20.7; IR (neat) 3087, 2982, 2889, 1738, 1607, 1521, 1353, 1221, 1036, 998, 926, 852, 783, 747, 712; MS (EI, 70 eV) *m*/*z* (%) 174 (5), 163 (11), 146 (25), 134 (24), 115 (21), 104 (7), 91 (13), 77 (12), 65 (6), 55 (9), 43 (100); HRMS (ESI) calcd for $C_{12}H_{13}NO_4Na$ 258.0737, found 258.0743.

**2-(2-Nitrophenyl)but-3-en-1-yl pivalate (6c).** A solution of pivalic acid (3.04 g, 29.76 mmol) in dry $CH_2Cl_2$ (8 mL) was added to a solution of DCC (6.41 g, 31.06 mmol) and DMAP (1.58 g, 12.94 mmol) in dry $CH_2Cl_2$ (18 mL) at rt under argon. After 15 min, a solution of **5** (2.50 g, 12.94 mmol) in dry $CH_2Cl_2$ (5 mL) was added dropwise. The mixture was stirred at reflux for 4 h, then cooled down to rt and filtered through a pad of Celite (rinsed with $CH_2Cl_2$). The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 98:2) gave **6c** (3.59 g, 12.94 mmol, 100%) as a yellow liquid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.81 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.60−7.53 (m, 1H), 7.46 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.39 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 6.05−5.91 (m, 1H), 5.24 (d, *J* = 10.5 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 4.40−4.35 (m, 3H), 1.07 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.1, 150.4, 135.8, 134.7, 132.5, 129.7, 127.7, 124.4, 117.9, 65.8, 42.5, 38.7, 27.0 (3C); IR (neat) 3073, 2970, 2907, 1726, 1640, 1608, 1578, 1525, 1480, 1397, 1352, 1280, 1143, 1035, 986, 924, 853, 782, 747; MS (EI, 70 eV) *m*/*z* (%) 174 (4), 163 (10), 146 (20), 145 (23), 134 (16), 130 (16), 115 (14), 91 (5), 85 (13), 77 (7), 65 (4), 57 (100), 55 (6), 41 (24); HRMS (ESI) calcd for $C_{15}H_{20}NO_4$ 278.1387, found 278.1394.

**2-(2-Aminophenyl)but-3-en-1-yl acetate (7b).** To a solution of **6b** (758 mg, 3.22 mmol) in AcOEt (65 mL) at rt under argon was added $SnCl_2{\cdot}2H_2O$ (3.63 g, 16.11 mmol) in one portion. The mixture was stirred at reflux for 4 h, then cooled down to rt and basified with saturated aqueous $NaHCO_3$ to pH 8−9. The two layers were separated, and the aqueous layer was extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography ($CH_2Cl_2$/AcOEt 99:1) gave **7b** (494 mg, 2.41 mmol, 75%) as a yellowish oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.11−7.02 (m, 2H), 6.76 (td, *J* = 7.5, 1.1 Hz, 1H), 6.72−6.67 (m, 1H), 5.98 (ddd, *J* = 17.2, 10.5, 6.6 Hz, 1H), 5.28−5.16 (m, 2H), 4.43 (dd, *J* = 11.1, 5.6 Hz, 1H), 4.22 (dd, *J* = 11.1, 8.5 Hz, 1H), 3.94 (br s, 2H), 3.81−3.71 (m, 1H), 2.06 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.5, 144.7, 136.8, 127.8, 127.7, 124.1, 118.8, 117.0, 116.4, 65.8, 42.8, 21.0; IR (neat) 3451 (br), 3370 (br), 3078, 3030, 2968, 1725, 1626, 1495, 1455, 1381, 1229, 1159, 1031, 997, 920, 747; MS (EI, 70 eV) *m*/*z* (%) 205 ($M^+$, 10), 145 (38), 144 (51), 132 (100), 130 (34), 117 (52), 115 (29), 105 (9), 91 (11), 77


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(11), 65 (8), 51 (6), 43 (39); HRMS (ESI) calcd for $C_{12}H_{16}NO_2$ 206.1176, found 206.1184.

**2-(2-Aminophenyl)but-3-en-1-yl pivalate (7c).** To a solution of **6c** (3.45 g, 12.43 mmol) in EtOH (30 mL) at rt under argon was added $SnCl_2{\cdot}2H_2O$ (14.02 g, 62.15 mmol) in one portion. The mixture was stirred at rt for 1 h, then 60 °C for another hour. The reaction mixture was cooled to rt, and water (10 mL) was added. Solid $NaHCO_3$ was carefully added until the solution was basic. The mixture was then filtered to remove the solids formed (rinsed with AcOEt), and the filtrate was extracted with AcOEt (5 × 10 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product **7c** (3.04 g, 12.29 mmol, 99%) was obtained as an orange oil and was used in the next step without further purification: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.10−7.05 (m, 2H), 6.78−6.72 (m, 1H), 6.69 (d, $J$ = 7.6 Hz, 1H), 6.00 (ddd, $J$ = 17.2, 10.5, 6.7 Hz, 1H), 5.28−5.17 (m, 2H), 4.45 (dd, $J$ = 11.1, 5.2 Hz, 1H), 4.15 (dd, $J$ = 11.1, 8.9 Hz, 1H), 4.00 (br s, 2H), 3.81−3.70 (m, 1H), 1.17 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 179.1, 144.7, 136.9, 127.80, 127.76, 124.0, 118.6, 117.0, 116.2, 65.5, 42.9, 38.8, 27.1 (3C); IR (neat) 3447 (br), 3376 (br), 3082, 2970, 2915, 2872, 1715, 1634, 1495, 1480, 1456, 1397, 1284, 1152, 1033, 976, 917, 747; MS (EI, 70 eV) $m/z$ (%) 247 ($M^+$, 12), 146 (17), 145 (68), 144 (76), 132 (100), 130 (35), 117 (25), 115 (11), 91 (4), 77 (5), 57 (48), 41 (7); HRMS (ESI) calcd for $C_{15}H_{22}NO_2$ 248.1645, found 248.1636.

**2-(2-Azidophenyl)but-3-en-1-yl acetate (1b).** The compound was prepared with the same procedure as for **1a**, from **7b** (385 mg, 1.87 mmol), *t*-BuONO (90% purity, 0.37 mL, 2.81 mmol), and $TMSN_3$ (0.29 mL, 2.25 mmol) in dry $CH_3CN$ (8.5 mL). Purification by flash column chromatography (pentane/$Et_2O$ 99:1 then 90:10) gave **1b** (412 mg, 1.78 mmol, 95%) as a yellowish liquid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.33−7.08 (m, 4H), 5.98 (ddd, $J$ = 17.2, 10.4, 7.0 Hz, 1H), 5.17 (dt, $J$ = 10.4, 1.4 Hz, 1H), 5.11 (dt, $J$ = 17.2, 1.4 Hz, 1H), 4.36 (dd, $J$ = 10.8, 7.6 Hz, 1H), 4.23 (dd, $J$ = 10.8, 6.5 Hz, 1H), 4.08−3.99 (m, 1H), 2.01 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.9, 138.0, 136.9, 131.6, 129.0, 128.2, 125.0, 118.4, 117.0, 65.9, 42.6, 20.9; IR (neat) 3073, 2964, 2894, 2121, 1738, 1639, 1581, 1488, 1284, 1222, 1033, 994, 919, 750; MS (EI, 70 eV) $m/z$ (%) 203 ($M^+ - N_2$, 3), 144 (24), 143 (100), 130 (67), 115 (14), 103 (17), 89 (5), 77 (25), 63 (4), 51 (10), 43 (44); HRMS (ESI) calcd for $C_{12}H_{13}N_3O_2Na$ 254.0900, found 254.0907.

**2-(2-Azidophenyl)but-3-en-1-yl pivalate (1c).** The compound was prepared with the same procedure as for **1a**, from **7c** (2.93 g, 11.87 mmol), *t*-BuONO (90% purity, 2.35 mL, 17.77 mmol), and $TMSN_3$ (1.87 mL, 14.24 mmol) in dry $CH_3CN$ (69 mL). Purification by flash column chromatography (pentane/$Et_2O$ 98:2) gave **1c** (3.08 g, 11.25 mmol, 95%) as a yellowish liquid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.32−7.20 (m, 2H), 7.18−7.07 (m, 2H), 5.98 (ddd, $J$ = 17.3, 10.4, 7.0 Hz, 1H), 5.20−5.10 (m, 2H), 4.35−4.22 (m, 2H), 4.09−4.02 (m, 1H), 1.11 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.3, 138.0, 136.8, 131.7, 129.1, 128.1, 124.8, 118.3, 116.9, 65.6, 42.7, 38.7, 27.1 (3C); IR (neat) 2971, 2898, 2123, 2100, 1726, 1639, 1581, 1488, 1480, 1450, 1396, 1363, 1280, 1145, 1033, 988, 919, 750; MS (EI, 70 eV) $m/z$ (%) 245 ($M^+ - N_2$, 2), 144 (27), 143 (100), 130 (39), 115 (8), 103 (5), 91 (2), 77 (5), 57 (22), 41 (6); HRMS (ESI) calcd for $C_{15}H_{19}N_3O_2Na$ 296.1369, found 296.1369.

**Ethyl 3-(3-methylindolin-2-yl)propanoate (8a).** To an open-to-air solution of **1a** (90 mg, 0.52 mmol) and ethyl iodoacetate (41 $\mu$L, 0.35 mmol) in toluene (2.2 mL) at rt, in a two-neck 10 mL round-bottom flask, was added a 1 M solution of $Et_3B$ in hexane (1.04 mL, 1.04 mmol) with a syringe. ***Caution:*** *The needle should be immersed into the reaction mixture in order to avoid a direct contact of $Et_3B$ drops with air.* The reaction mixture was stirred at rt for 1 h, then $Et_3B$ (0.35 mL, 0.35 mmol) was added. The reaction mixture was stirred for 3 h, saturated aq $NaHCO_3$ (5 mL) was added to the mixture, and the two layers were separated. The aqueous layer was extracted with $Et_2O$ (3 × 4 mL). The combined organic layers were washed with brine (1 × 5 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 7:1) gave **8a** (71 mg, 0.30 mmol, 87%, *trans*/*cis* 83:17 as determined by $^1$H NMR). The diastereomers were separated by a second flash column chromatography ($CH_2Cl_2$/AcOEt 99:1 to 0:100). Major diastereomer (*trans*), yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.06−6.98 (m, 2H), 6.76−6.69 (m, 1H), 6.64−6.58 (m, 1H), 4.16 (q, $J$ = 7.2 Hz, 2H), 3.99 (br s, 1H), 3.44−3.39 (m, 1H), 3.00−2.87 (m, 1H), 2.46 (t, $J$ = 7.5 Hz, 2H), 2.13−1.99 (m, 1H), 1.95−1.81 (m, 1H), 1.32 (d, $J$ = 6.8 Hz, 3H), 1.26 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.5, 150.2, 133.8, 127.4, 123.3, 118.7, 109.2, 67.3, 60.5, 42.3, 31.3, 30.4, 18.1, 14.2; IR (neat) 3364 (br), 2957, 2929, 2867, 1725, 1609, 1483, 1465, 1368, 1243, 1159, 1094, 1030, 746; MS (EI, 70 eV) $m/z$ (%) 233 ($M^+$, 8), 187 (5), 144 (14), 132 (100), 117 (31), 103 (7), 90 (6), 77 (10), 55 (9); HRMS (ESI) calcd for $C_{14}H_{20}NO_2$ 234.1489, found 234.1481. Minor diastereomer (*cis*), yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.10−6.99 (m, 2H), 6.74 (td, $J$ = 7.4, 1.0 Hz, 1H), 6.65 (d, $J$ = 7.7 Hz, 1H), 4.20−4.07 (m, 3H), 3.83−3.74 (m, 1H), 3.33−3.23 (m, 1H), 2.45−2.38 (m, 2H), 2.01−1.83 (m, 2H), 1.26 (t, $J$ = 7.1 Hz, 3H), 1.16 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.3, 149.7, 134.8, 127.4, 123.8, 119.0, 109.4, 62.2, 60.5, 39.1, 32.1, 25.9, 14.4, 14.2. IR (neat) 3369 (br), 2961, 2929, 1727, 1608, 1483, 1463, 1369, 1249, 1159, 1029, 740; MS (EI, 70 eV) $m/z$ (%) 233 ($M^+$, 6), 187 (6), 144 (14), 132 (100), 117 (32), 103 89), 90 (8), 77 (14), 55 (15); HRMS (ESI) calcd for $C_{14}H_{20}NO_2$ 234.1489, found 234.1483.

**Ethyl 3-(3-(acetoxymethyl)indolin-2-yl)propanoate (8b).** To an open-to-air solution of **1b** (89 mg, 0.39 mmol) and ethyl iodoacetate (30 $\mu$L, 0.26 mmol) in toluene (0.5 mL) at rt, in a two-neck 10 mL round-bottom flask, was added a 1 M solution of $Et_3B$ in hexane (0.77 mL, 0.77 mmol) with a syringe (***caution***, see **8a**). The reaction mixture was stirred at rt for 1 h, and $Et_3B$ (0.26 mL, 0.26 mmol) was added. After 1.5 h, $Et_3B$ (0.13 mL, 0.13 mmol) was added, and the reaction mixture was stirred for 2 h. The same workup procedure as for **8a** was used. Purification by flash column chromatography (cyclohexane/AcOEt 5:1 then 4:1) gave **8b** (57 mg, 0.19 mmol, 75%, *trans*/*cis* 93:7 as determined by $^1$H NMR) as a yellow oil. The diastereomers were inseparable. Mixture of diastereomers: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.14−7.02 (m, 2H major), 6.71 (td, $J$ = 7.4, 0.8 Hz, 1H major), 6.61 (d, $J$ = 7.8 Hz, 1H major), 4.30 (dd, $J$ = 11.0, 5.9 Hz, 1H major), 4.21−4.10 (m, 3H major), 3.93 (br s, 1H major), 3.72−3.64 (m, 1H major), 3.50−3.44 (m, 1H minor), 3.30−3.22 (m, 1H major), 2.43 (t, $J$ = 7.5 Hz, 2H major), 2.09 (s, 3H major), 2.08 (s, 3H minor), 2.07−1.81 (m, 2H major), 1.25 (t, $J$ = 7.1 Hz, 3H major); IR (neat) 3373 (br), 2978, 2934, 1725, 1608, 1485, 1466, 1366, 1226, 1159, 1029, 749; HRMS (ESI) calcd for $C_{16}H_{22}NO_4$ 292.1543, found 292.1538. Major diastereomer (*trans*): $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.3, 170.9, 150.3, 128.4, 127.7, 124.6, 118.7, 109.4, 66.2, 61.8, 60.5, 47.2, 31.4, 30.8, 20.9, 14.2; MS (EI, 70 eV) $m/z$ (%) 291 ($M^+$, 10), 231 (13), 186 (12), 144 (17), 130 (100), 117 (15), 103 (4), 55 (11), 43 (10). Minor diastereomer (*cis*): MS (EI, 70 eV) $m/z$ (%) 291 ($M^+$, 8), 231 (19), 186 (10), 144 (22), 130 (100), 117 (16), 103 (4), 55 (15), 43 (15).

**(2-(3-Ethoxy-3-oxopropyl)indolin-3-yl)methyl pivalate (8c).** To an open-to-air solution of **1c** (113 mg, 0.41 mmol) and ethyl iodoacetate (33 $\mu$L, 0.28 mmol) in toluene (0.5 mL) at rt, in a two-neck 10 mL round-bottom flask, was added a 1 M solution of $Et_3B$ in hexane (0.83 mL, 0.83 mmol) with a syringe (***caution***, see **8a**). The reaction mixture was stirred at rt for 1 h, and $Et_3B$ (0.28 mL, 0.28 mmol) was added. After 1 h, $Et_3B$ (0.28 mL, 0.28 mmol) was added, and the reaction mixture was stirred for 2 h. The same workup procedure as for **8a** was used. Purification by flash column chromatography (cyclohexane/AcOEt 7:1) gave **8c** (65 mg, 0.19 mmol, 70%, *trans*/*cis* 97:3 as determined by GC) as a yellow oil. The diastereomers were inseparable. Mixture of diastereomers: IR (neat) 3370 (br), 2976, 2915, 1724, 1608, 1484, 1465, 1397, 1367, 1281, 1253, 1147, 1032, 747; HRMS (ESI) calcd for $C_{19}H_{28}NO_4$ 334.2013, found 334.2016; GC $t_R$ (major) 23.53 min, $t_R$ (minor) 23.92 min (60 °C, 0 min, 60−280 °C, 8 °C/min, 280 °C, 15 min). Major diastereomer (*trans*): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.12 (d, $J$ = 7.4 Hz, 1H), 7.05 (t, $J$ = 7.8 Hz, 1H), 6.70 (td, $J$ = 7.4, 0.8 Hz, 1H), 6.60 (d, $J$ = 7.8 Hz, 1H), 4.28−4.17 (m, 2H), 4.15 (q, $J$ = 7.1 Hz, 2H), 3.95 (br s, 1H), 3.72−3.64 (m, 1H), 3.30−3.22 (m, 1H), 2.43 (t, $J$ =


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7.4 Hz, 2H), 2.09−1.95 (m, 1H), 1.94−1.80 (m, 1H), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.21 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.4, 173.3, 150.4, 128.4, 127.7, 124.7, 118.6, 109.4, 66.2, 61.8, 60.5, 47.4, 38.8, 31.4, 30.9, 27.2 (3C), 14.2; MS (EI, 70 eV) $m/z$ (%) 333 ($M^+$, 6), 231 (25), 186 (22), 185 (39), 184 (72), 144 (21), 130 (100), 117 (12), 77 (8), 55 (21). Minor diastereomer (*cis*): MS (EI, 70 eV) $m/z$ (%) 333 ($M^+$, 5), 231 (27), 186 (20), 185 (51), 184 (100), 144 (32), 130 (89), 117 (19), 77 (10), 57 (40).

**(3-Oxo-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-methyl acetate (9b).** To a solution of **8b** [48 mg, 0.17 mmol, *trans*/*cis* (93:7) as determined by $^1$H NMR] in dry toluene (1.5 mL) was added (+)-camphor-10-sulfonic acid (CSA) (8 mg, 0.03 mmol). The mixture was stirred at reflux for 2 h, cooled to rt, and the solvent was removed under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 3:2) gave **9b** (34 mg, 0.14 mmol, 82%, *trans*/*cis* 99:1 as determined by GC) as a white solid. The diastereomers were not completely separable. Mixture of diastereomers: mp 115−119 °C; IR (neat) 2973, 2907, 1736, 1695, 1602, 1482, 1463, 1401, 1364, 1236, 1126, 1034, 755; HRMS (ESI) calcd for $C_{14}H_{15}NO_3Na$ 268.0944, found 268.0943; GC $t_R$ (major) 23.72 min; $t_R$ (minor) 23.47 min (60 °C, 0 min, 60−280 °C, 8 °C/min, 280 °C, 15 min). Major diastereomer (*trans*): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.63 (d, $J$ = 7.8 Hz, 1H), 7.31−7.24 (m, 1H), 7.20 (d, $J$ = 7.6 Hz, 1H), 7.08 (t, $J$ = 7.6 Hz, 1H), 4.60 (dd, $J$ = 11.1, 5.3 Hz, 1H), 4.46−4.35 (m, 1H), 4.30 (dd, $J$ = 11.1, 8.5 Hz, 1H), 3.58−3.48 (m, 1H), 2.93−2.79 (m, 1H), 2.61 (dd, $J$ = 16.6, 8.4 Hz, 1H), 2.54−2.42 (m, 1H), 2.11 (s, 3H), 2.10−2.00 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.3, 170.7, 139.4, 133.5, 128.6, 124.4, 124.3, 115.0, 67.4, 65.2, 48.0, 36.0, 28.7, 20.8; MS (EI, 70 eV) $m/z$ (%) 245 ($M^+$, 8), 185 (48), 184 (100), 172 (15), 156 (9), 130 (40), 117 (11), 103 (8), 77 (9), 55 (75), 43 (23). Minor diastereomer (*cis*): MS (EI, 70 eV) $m/z$ (%) 245 ($M^+$, 10), 185 (50), 184 (100), 172 (11), 156 (9), 130 (51), 117 (11), 103 (5), 77 (9), 55 (56), 43 (21).

**(3-Oxo-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl)-methyl pivalate (9c).** The compound was prepared using the same procedure as for **9b**, from **8c** (1.30 g, 3.90 mmol, *trans*/*cis* 97:3 as determined by GC) and CSA (181 mg, 0.78 mmol) in dry toluene (35 mL). Purification by flash column chromatography (cyclohexane/AcOEt 4:1) gave **9c** (969 mg, 3.37 mmol, 86%, *trans*/*cis* > 99:1 as determined by GC) as a white solid. The diastereomers were not completely separable. Mixture of diastereomers: mp 84−86 °C; IR (neat) 2971, 2875, 1725, 1698, 1601, 1479, 1460, 1397, 1351, 1282, 1155, 757; HRMS (ESI) calcd for $C_{17}H_{22}NO_3$ 288.1594, found 288.1589; GC $t_R$ (major) 23.95 min, $t_R$ (minor) 23.71 min (60 °C, 0 min, 60−280 °C, 8 °C/min, 280 °C, 15 min). Major diastereomer (*trans*): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.63 (d, $J$ = 7.8 Hz, 1H), 7.31−7.24 (m, 1H), 7.20 (d, $J$ = 7.5 Hz, 1H), 7.07 (td, $J$ = 7.5, 0.9 Hz, 1H), 4.57 (dd, $J$ = 11.1, 5.0 Hz, 1H), 4.45−4.37 (m, 1H), 4.30 (dd, $J$ = 11.1, 8.6 Hz, 1H), 3.58−3.48 (m, 1H), 2.94−2.80 (m, 1H), 2.61 (dd, $J$ = 16.5, 8.3 Hz, 1H), 2.55−2.45 (m, 1H), 2.14−1.98 (m, 1H), 1.21 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.3, 171.4, 139.4, 133.5, 128.6, 124.4, 124.3, 115.1, 67.7, 65.2, 48.2, 38.9, 36.0, 28.7, 27.2 (3C); MS (EI, 70 eV) $m/z$ (%) 287 ($M^+$, 2), 186 (10), 185 (44), 184 (100), 172 (6), 156 (5), 130 (14), 117 (3), 103 (3), 77 (4), 57 (16), 55 (30). Minor diastereomer (*cis*): MS (EI, 70 eV) $m/z$ (%) 287 ($M^+$, 2), 186 (11), 185 (42), 184 (100), 172 (11), 156 (8), 130 (21), 117 (8), 103 (7), 77 (8), 57 (22), 55 (39).

**2,4-Dimethoxy-3-methylbenzaldehyde (10).** The compound was prepared according to Zhu's procedure[22] from 2,6-dimethoxytoluene (3.88 g, 25.00 mmol) and $POCl_3$ (2.80 mL, 30.60 mmol) in dry DMF (10 mL). Purification by flash column chromatography (cyclohexane/AcOEt 10:1) gave **10** (3.20 g, 17.77 mmol, 71%) as a yellowish solid. Physical and spectral data were in accordance with literature data:[22] mp 52−55 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.23 (s, 1H), 7.74 (d, $J$ = 8.7 Hz, 1H), 6.75 (d, $J$ = 8.7 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.16 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 189.1, 164.0, 162.6, 128.0, 122.8, 120.1, 106.5, 63.2, 55.9, 8.5; HRMS (ESI) calcd for $C_{10}H_{13}O_3$ 181.0859, found 181.0864.

**2,4-Dimethoxy-3-methylphenol (11).** The compound was prepared according to Zhu's procedure[22] from **10** (2.08 g, 11.55 mmol) and *m*-CPBA (77% purity, 3.88 g, 17.33 mmol) in dry $CH_2Cl_2$ (23 mL) for the oxidation step followed by 10% KOH (7.80 mL, 13.86 mmol) in MeOH (5 mL) for the saponification step. Purification by flash column chromatography (cyclohexane/AcOEt 10:1) gave **11** (1.62 g, 9.63 mmol, 83%) as a yellowish solid. Physical and spectral data were in accordance with literature data:[22] mp 32−34 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.75 (d, $J$ = 8.8 Hz, 1H), 6.54 (d, $J$ = 8.8 Hz, 1H), 5.25 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.17 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 151.9, 146.0, 142.9, 120.0, 111.6, 106.8, 60.8, 56.1, 9.3; MS (EI, 70 eV) $m/z$ (%) 169 (9), 168 ($M^+$, 100), 153 (78), 138 (8), 125 (52), 110 (21), 93 (9), 79 (11), 65 (20), 53 (11).

**(*E*)-1-((4-Bromobut-2-en-1-yl)oxy)-2,4-dimethoxy-3-methylbenzene (12).** To a solution of **11** (2.09 g, 12.43 mmol) in acetone (63 mL) at rt under argon was added *trans*-1,4-dibromo-2-butene (13.29 g, 62.14 mmol) followed by $K_2CO_3$ (3.43 g, 24.86 mmol). The reaction mixture was refluxed for 18 h. The mixture was cooled to rt, $K_2CO_3$ was removed by filtration (rinsed with acetone), and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 30:1) gave **12** (3.03 g, 10.06 mmol, 81%) as a yellowish liquid: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.69 (d, $J$ = 8.9 Hz, 1H), 6.51 (d, $J$ = 8.9 Hz, 1H), 6.13−5.95 (m, 2H), 4.54 (d, $J$ = 4.1 Hz, 2H), 3.99 (d, $J$ = 6.4 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 2.15 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 153.0, 148.9, 145.8, 130.8, 128.8, 121.3, 112.0, 105.2, 69.0, 60.4, 55.9, 31.8, 8.9; IR (neat) 2999, 2934, 2832, 1593, 1483, 1462, 1377, 1254, 1221, 1205, 1108, 1061, 1023, 964, 787; MS (EI, 70 eV) $m/z$ (%) 302 (5), 300 ($M^+$, 5), 220 (4), 168 (17), 167 (100), 139 (31), 124 (23), 107 (17), 91 (6), 79 (7), 65 (5), 53 (19); HRMS (ESI) calcd for $C_{13}H_{18}BrO_3$ 301.0439, found 301.0441.

**(*E*)-1-((4-(Benzyloxy)but-2-en-1-yl)oxy)-2,4-dimethoxy-3-methylbenzene (13).** To a solution of benzyl alcohol (0.45 mL, 4.32 mmol) in dry THF (21 mL) at 0 °C under argon was added NaH (55% dispersion in oil, 290 mg, 6.64 mmol) portionwise. The mixture was stirred at rt for 30 min, then a solution of **12** (1.00 g, 3.32 mmol) in dry THF (5 mL) was added at 0 °C followed by tetrabutylammonium iodide (92 mg, 0.25 mmol) after 10 min. The mixture was stirred at rt for 18 h. $Et_2O$ (10 mL) was added followed by water dropwise (5 mL) and brine (5 mL). The two layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with brine (1 × 5 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 15:1) gave **13** (937 mg, 2.85 mmol, 86%) as a yellowish oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.37−7.26 (m, 5H), 6.71 (d, $J$ = 8.9 Hz, 1H), 6.50 (d, $J$ = 8.9 Hz, 1H), 6.05−5.90 (m, 2H), 4.56−4.52 (m, 2H), 4.52 (s, 2H), 4.10−4.04 (m, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 2.15 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 152.9, 148.9, 146.0, 138.2, 129.6, 128.6, 128.4 (2C), 127.8 (2C), 127.6, 121.2, 111.9, 105.2, 72.2, 70.0, 69.5, 60.4, 55.9, 8.9; IR (neat) 2935, 2855, 1592, 1484, 1454, 1359, 1254, 1222, 1107, 1058, 1025, 967, 788, 734, 696; MS (EI, 70 eV) $m/z$ (%) 328 ($M^+$, 27), 237 (39), 220 (44), 207 (35), 176 (19), 175 (100), 147 (40), 105 (13), 91 (77), 77 (13), 65 (11); HRMS (ESI) calcd for $C_{20}H_{24}O_4Na$ 351.1567, found 351.1574.

**6-(1-(Benzyloxy)but-3-en-2-yl)-2,4-dimethoxy-3-methylphenol (14).** A solution of **13** (900 mg, 2.74 mmol) in *N*,*N*-diethylaniline (15 mL) at rt was thoroughly degassed with argon for 5 min under a slight vacuum. The mixture was then stirred at 215 °C for 4 h. The mixture was cooled to rt, diluted with AcOEt (10 mL), and acidified with 1 N HCl to pH 1−2. The aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 20:1) gave **14** (819 mg, 2.49 mmol, 91%) as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36−7.26 (m, 5H), 6.42 (s, 1H), 6.11 (ddd, $J$ = 17.2, 10.5, 6.8 Hz, 1H), 6.00 (br s, 1H), 5.20−5.16 (m, 1H), 5.13 (dt, $J$ = 10.5, 1.5 Hz, 1H), 4.56 (s, 2H), 4.03−3.94 (m, 1H), 3.82−3.70 (m, 8H), 2.14 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.3, 146.5, 141.2, 138.1, 137.8, 128.3 (2C), 127.7 (2C), 127.6, 124.8, 118.3, 116.0, 106.6, 73.2, 73.1, 60.7, 56.1, 44.2, 9.2; IR (neat) 3322 (br), 2938, 2858, 2832, 1595, 1488, 1455, 1412, 1357, 1186, 1119, 1021, 997, 915, 735,


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697; MS (EI, 70 eV) *m*/*z* (%) 328 ($M^+$, 22), 237 (35), 220 (33), 207 (26), 176 (19), 175 (100), 147 (39), 115 (7), 91 (58), 65 (10); HRMS (ESI) calcd for $C_{20}H_{25}O_4$ 329.1747, found 329.1748.

**6-(1-(Benzyloxy)but-3-en-2-yl)-2,4-dimethoxy-3-methylphenyl acetate (15).** To a solution of **14** (668 mg, 2.03 mmol) in dry pyridine (3.5 mL) at 0 °C under argon was added $Ac_2O$ (0.61 mL, 6.36 mmol) dropwise. The reaction mixture was stirred at rt for 4 h, then diluted with water (5 mL) and $Et_2O$ (5 mL). The aqueous layer was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with 1 N HCl (3 × 3 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 15:1) gave **15** (715 mg, 1.93 mmol, 95%) as a yellowish oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36−7.26 (m, 5H), 6.48 (s, 1H), 5.99 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H), 5.18−5.08 (m, 2H), 4.52 (s, 2H), 3.82−3.76 (m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.70−3.63 (m, 2H), 2.29 (s, 3H), 2.12 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.3, 156.1, 150.6, 138.3, 137.9, 136.1, 131.4, 128.3 (2C), 127.7 (2C), 127.6, 119.4, 116.3, 105.3, 73.1, 72.7, 60.7, 55.7, 43.3, 20.6, 9.1; IR (neat) 2937, 2855, 1761, 1585, 1483, 1455, 1407, 1366, 1181, 1125, 1024, 1002, 897, 735, 698; MS (EI, 70 eV) *m*/*z* (%) 370 ($M^+$, 3), 328 (45), 298 (13), 249 (15), 237 (25), 220 (26), 207 (47), 175 (100), 147 (21), 91 (95), 65 (13), 43 (22); HRMS (ESI) calcd for $C_{22}H_{27}O_5$ 371.1853, found 371.1851.

**3-Amino-2-(1-(benzyloxy)but-3-en-2-yl)-4,6-dimethoxy-5-methylphenyl acetate (16).** To a solution of **15** (481 mg, 1.30 mmol) in $Ac_2O$ (6.9 mL) at rt was added a solution of $Hg(OAc)_2$ (41 mg, 0.13 mmol) in glacial AcOH (3.4 mL). The reaction mixture was cooled to 0 °C, then 100% fuming $HNO_3$ (0.31 mL, 7.34 mmol) was added dropwise over 5 min. The mixture was stirred at 0 °C for 20 min, then poured over ice water (38 mL) and extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were washed with 5% aqueous $K_2CO_3$ until pH 7, then with brine (1 × 10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure at 30 °C. The crude nitro compound was dissolved in MeOH (3.4 mL), and 36% HCl (3.4 mL) was added dropwise. The mixture was stirred at rt for 15 min, then Zn dust (1.27 g, 19.46 mmol) was added portionwise in such a way to maintain a vigorous, but not violent, refluxing reaction. When the addition was finished, the mixture was stirred at rt for 1 h then filtered through a plug of cotton (rinsed with $CH_2Cl_2$ then AcOEt). The filtrate was diluted with AcOEt (58 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic layer was washed with brine (1 × 10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 5:1) gave **16** (365 mg, 0.95 mmol, 73%) as an orange oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38−7.23 (m, 5H), 6.20−6.08 (m, 1H), 5.23−5.12 (m, 2H), 4.51 (s, 2H), 4.21 (br s, 2H), 3.99−3.88 (m, 2H), 3.81−3.72 (m, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.2, 144.2, 142.2, 139.5, 138.2, 136.4, 135.7, 128.4 (2C), 127.6 (3C), 123.8, 117.5, 115.8, 73.2, 71.4, 60.8, 59.5, 40.9, 20.7, 9.6; IR (neat) 3433 (br), 3349 (br), 2935, 2855, 1759, 1457, 1415, 1366, 1258, 1195, 1054, 1009, 894, 735, 697; MS (EI, 70 eV) *m*/*z* (%) 385 ($M^+$, 37), 343 (19), 328 (28), 264 (15), 222 (57), 220 (41), 206 (21), 192 (19), 108 (20), 91 (100), 79 (23), 65 (13), 43 (19); HRMS (ESI) calcd for $C_{22}H_{28}NO_5$ 386.1962, found 386.1952.

**3-Azido-2-(1-(benzyloxy)but-3-en-2-yl)-4,6-dimethoxy-5-methylphenyl acetate (17).** The compound was prepared according to the same procedure as for **1a**, from **16** (352 mg, 0.91 mmol), *t*-BuONO (90% purity, 0.18 mL, 1.37 mmol), and $TMSN_3$ (0.15 mL, 1.10 mmol) in dry $CH_3CN$ (8.5 mL). Purification by flash column chromatography (pentane/$Et_2O$ 5:1) gave **17** (286 mg, 0.69 mmol, 76%) as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36−7.23 (m, 5H), 6.07 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.11−5.08 (m, 1H), 5.05 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.52 (s, 2H), 4.16−4.07 (m, 1H), 3.87 (t, *J* = 8.7 Hz, 1H), 3.79 (s, 3H), 3.72−3.65 (m, 1H), 3.68 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.6, 151.2, 148.1, 139.7, 138.4, 137.0, 128.3 (2C), 127.7, 127.6 (2C), 127.5, 125.3, 125.1, 116.0, 72.8, 71.4, 61.2, 60.7, 42.2, 20.7, 9.6; IR (neat) 2939, 2863, 2108, 1770, 1454, 1406, 1367, 1269, 1188, 1105, 1027, 995, 896, 735, 698; MS (EI, 70 eV) *m*/*z* (%) 383 ($M^+ - N_2$, 8), 341 (11), 326 (12), 262 (11), 250 (15), 220 (74), 205 (26), 190 (31), 176 (15), 160 (22), 117 (5), 91 (100), 65 (13), 43 (28); HRMS (ESI) calcd for $C_{22}H_{25}N_3O_5Na$ 434.1686, found 434.1678.

**Ethyl 3-(4-acetoxy-3-((benzyloxy)methyl)-5,7-dimethoxy-6-methylindolin-2-yl)propanoate (18).** To an open-to-air solution of **17** (262 mg, 0.64 mmol) and ethyl iodoacetate (50 μL, 0.43 mmol) in toluene (0.9 mL) at rt, in a two-neck 10 mL round-bottom flask, was added a 1 M solution of $Et_3B$ in hexane (1.28 mL, 1.28 mmol) with a syringe (***caution***, see **8a**). The mixture was stirred at rt for 1 h, then $Et_3B$ (0.42 mL, 0.42 mmol) was added. After 1 h, $Et_3B$ (0.42 mL, 0.42 mmol) was added. The reaction mixture was stirred for 3 h then the same workup procedure as for **8a** was used. Purification by flash column chromatography (cyclohexane/AcOEt 4:1) gave **18** (160 mg, 0.34 mmol, 80%, *trans*/*cis* 97:3 as determined by $^1$H NMR) as a yellow oil. The diastereomers were inseparable. Mixture of diastereomers: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38−7.27 (m, 5H major), 4.51 (s, 2H major), 4.45 (s, 2H minor), 4.11 (q, *J* = 7.1 Hz, 2H major), 3.89−3.78 (m, 2H major), 3.70 (s, 3H major), 3.64 (s, 3H major), 3.64−3.59 (m, 1H major), 3.45 (t, *J* = 8.9 Hz, 1H major), 3.27−3.19 (m, 1H major), 2.40 (t, *J* = 7.6 Hz, 2H major), 2.18 (s, 6H minor), 2.15 (s, 6H major), 2.00−1.77 (m, 2H major), 1.23 (t, *J* = 7.1 Hz, 3H major); IR (neat) 3346 (br), 2986, 2934, 2850, 1762, 1728, 1627, 1473, 1367, 1255, 1198, 1058, 1009, 905, 752, 698; HRMS (ESI) calcd for $C_{26}H_{34}NO_7$ 472.2330, found 472.2310. Major diastereomer (*trans*): $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.4, 168.9, 142.5, 140.4, 140.0, 138.3, 137.4, 128.4 (2C), 127.7 (2C), 127.6, 125.0, 119.1, 73.1, 70.8, 62.6, 60.9, 60.4, 59.0, 48.0, 31.5, 30.7, 20.5, 14.2, 9.4; MS (EI, 70 eV) *m*/*z* (%) 472 (24), 471 ($M^+$, 100), 415 (21), 414 (95), 384 (11), 350 (22), 308 (33), 293 (19), 276 (63), 230 (11), 204 (20). Minor diastereomer (*cis*): MS (EI, 70 eV) *m*/*z* (%) 472 (27), 471 ($M^+$, 100), 415 (16), 414 (65), 384 (5), 350 (20), 308 (31), 293 (29), 276 (85), 230 (19), 204 (23).

**9-((Benzyloxy)methyl)-5,7-dimethoxy-6-methyl-3-oxo-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-8-yl acetate (19).** The compound was prepared according to the same procedure as for **9b**, from **18** (115 mg, 0.24 mmol, *trans*/*cis* 97:3 as determined by $^1$H NMR) and CSA (12 mg, 0.06 mmol) in dry toluene (2.5 mL) for 3 h. Purification by flash column chromatography (cyclohexane/AcOEt 3:2) gave **19** (90 mg, 0.21 mmol, 87%, *trans*/*cis* 97:3 as determined by $^1$H NMR) as an orange oil. The diastereomers were inseparable. Mixture of diastereomers: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.41−7.28 (m, 5H major), 4.59 (s, 2H minor), 4.54 (s, 2H major), 4.51−4.41 (m, 1H major), 3.99−3.88 (m, 1H major), 3.81 (s, 3H major), 3.68 (s, 3H minor), 3.65 (s, 3H major), 3.51−3.40 (m, 2H major), 2.96−2.81 (m, 1H major), 2.62−2.46 (m, 2H major), 2.23 (s, 3H minor), 2.20 (s, 3H major), 2.14 (s, 3H major), 2.12−2.03 (m, 1H major); IR (neat) 2934, 2863, 1766, 1707, 1614, 1470, 1453, 1417, 1367, 1288, 1195, 1119, 1069, 1010, 746, 699; HRMS (ESI) calcd for $C_{24}H_{28}NO_6$ 426.1911, found 426.1902. Major diastereomer (*trans*): $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.4, 168.6, 148.0, 146.2, 137.9, 136.2, 128.5 (2C), 128.0, 127.8, 127.6 (2C), 126.3, 126.2, 73.3, 70.0, 69.7, 60.8, 59.6, 49.4, 35.2, 27.6, 20.4, 10.1; MS (EI, 70 eV) *m*/*z* (%) 426 (9), 425 ($M^+$, 42), 384 (18), 383 (67), 293 (18), 292 (100), 264 (31), 230 (33), 204 (9). Minor diastereomer (*cis*): MS (EI, 70 eV) *m*/*z* (%) 426 (12), 425 ($M^+$, 63), 384 (19), 383 (78), 293 (15), 292 (91), 262 (38), 247 (39), 230 (100), 204 (20). **One-pot radical cascade/lactamization:** To an open-to-air solution of **17** (193 mg, 0.47 mmol) and ethyl iodoacetate (37 μL, 0.31 mmol) in toluene (0.7 mL) at rt, in a two-neck 10 mL round-bottom flask equipped with a condenser, was added a 1 M solution of $Et_3B$ in hexane (0.94 mL, 0.94 mmol) with a syringe (***caution***, see **8a**). The mixture was stirred at rt for 1 h then $Et_3B$ (0.31 mL, 0.31 mmol) was added. After 1 h, $Et_3B$ (0.31 mL, 0.31 mmol) was added. The reaction mixture was stirred for 2 h, then CSA (29 mg, 0.13 mmol) and 2 mL of toluene were added, and the mixture was refluxed for 4 h. The mixture was cooled to rt and then concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/AcOEt 3:2) gave **19** (107 mg, 0.25 mmol, 80%, *trans*/*cis* 97:3 as determined by $^1$H NMR) as an orange oil.


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## ■ ASSOCIATED CONTENT

### Supporting Information

Copies of $^{1}H$ and $^{13}C$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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