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Total Syntheses of Heliotridane and Pseudoheliotridane Through Nitrodiene–Acrylate 6π-Electrocyclization/[3+2] Cycloaddition

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Keywords

nitrodiene, 6π-electrocyclization/[3+2] cycloaddition, total synthesis, pyrrolizidine alkaloids, heliotridane, pseudoheliotridane

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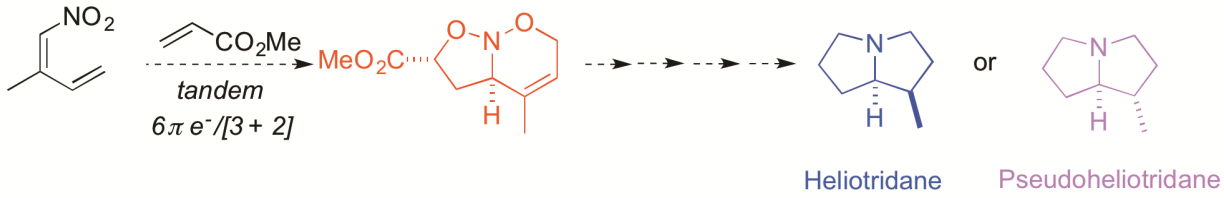
Koc and Kwon

Graphical Abstract



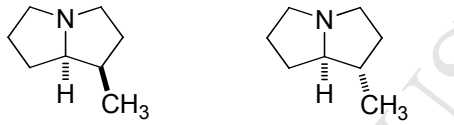
Abstract

The total syntheses of the pyrrolizidine alkaloids heliotridane and pseudoheliotridane have been accomplished in six steps (overall yields: 24 and 7%, respectively) using, for the first time, the tandem 6π-electrocyclization/[3+2] dipolar cycloaddition of an acyclic nitrodiene, 1-nitro-2-methyl-1,3-butadiene.

Introduction

Pyrrolizidine alkaloids are widespread in Nature and possess a diverse array of biological activities, including hepatotoxicity, pneumotoxicity, and nucleotoxicity (mutagenesis, carcinogenesis, and antimitotic effects).[1] These biological activities, in conjunction with often novel structures, have made the pyrrolizidine alkaloids popular synthetic targets for showcasing new synthetic methods and strategies.[2] With few exceptions,[3] the syntheses of pyrrolizidine alkaloids described to date have mainly relied on chiral pool materials as starting materials.[4] The tandem [4+2]/[3+2] cycloaddition process developed by Denmark has been applied successfully to the syntheses of a variety of pyrrolizidine alkaloids, including platynecine, rosmarinecine, crotanecine, australine, and 3-epiaustraline.[5] We recently developed[6] a new, general strategy, based on tandem 6π-electrocyclization of nitrodienes and

[3+2] cycloaddition of the resulting nitronates, to form nitroso acetals with well-defined stereochemistry. In this one-pot domino process, two rings are formed and one quaternary center is generated, with the products obtained predominantly as single diastereoisomers in good yields. Hydrogenolysis of the resulting nitroso acetals provides functionalized, synthetically useful, five-membered azacyclic ring systems with well-defined stereochemistry, suitable for the formation of pyrrolizidine alkaloids.



Heliotridane **1** Pseudoheliotridane **2**

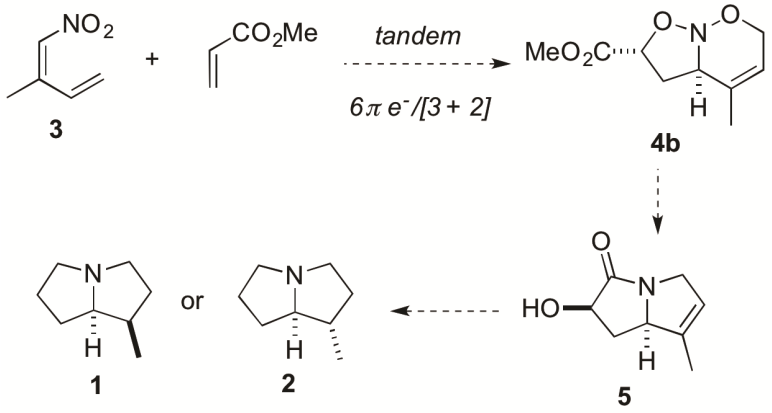
Figure 1. Heliotridane and pseudoheliotridane

The pyrrolizidine alkaloids heliotridane (**1**) and pseudoheliotridane (**2**) are natural products that have been isolated from various plant sources. Heliotridane has been obtained as a degradation product of a large number of alkaloids found in the *Senecio*, *Heliotrofiiuna*, *Crotalaria*, *Erechtites*, and *Trichodesma* genera. Pseudoheliotridane, a diastereoisomer of heliotridane, has been obtained from the alkaloids in *Trachelanthus korolkovi*.[7]

This paper describes the total syntheses of the pyrrolizidine alkaloids heliotridane and pseudoheliotridane using, for the first time, the tandem 6π-electrocyclization/[3+2] cycloaddition reaction developed for cyclic nitrodienes but, instead, applying an acyclic nitrodiene, 1-nitro-2-methyl-1,3-butadiene.

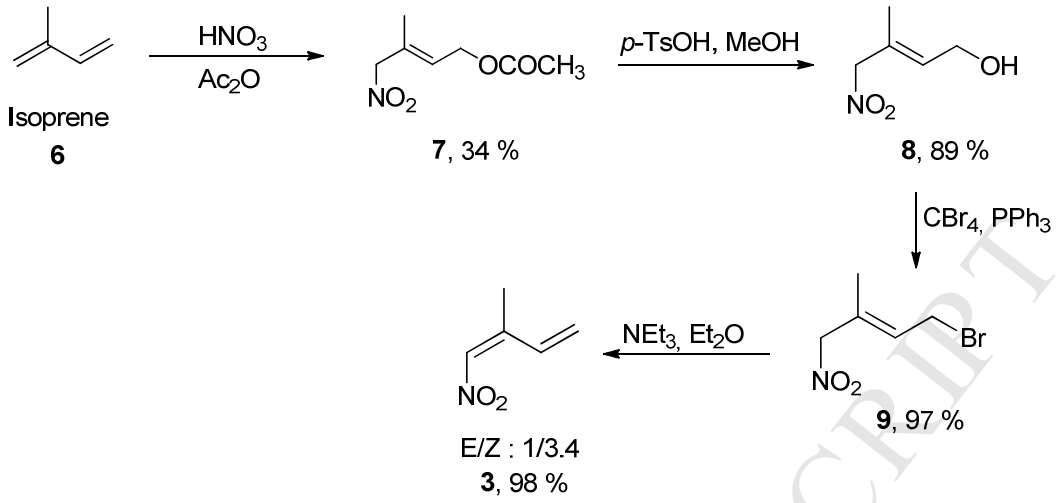
Results and Discussion

Scheme 1 illustrates the synthetic blueprint for heliotridane. We expected the tandem isomerization/6π-electrocyclization/[3+2] cycloaddition of 1-nitro-2-methyl-1,3-butadiene (**3**) with methyl acrylate to result in the nitroso acetal **4b**. According to our previous observations, we anticipated that treatment of this nitroso acetal with Raney nickel and H_2, and subsequent heating under reflux in toluene, would provide the bicyclic lactam **5**.[6] Sequential deoxygenation and reduction of **5** would then give the pyrrolizidine alkaloids heliotridane and pseudoheliotridane.



Scheme 1. Synthetic Plan for Heliotridane and Pseudoheliotridane

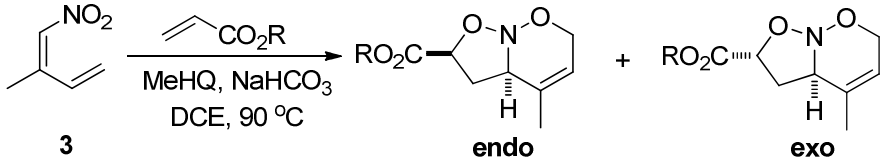
First, we synthesized 1-nitro-2-methyl-1,3-butadiene (**3**) from isoprene (**6**) in four steps through modification of known patent procedures.[8,9] Nitroacetylation of isoprene with HNO_3 and Ac_2O gave 3-methyl-4-nitrobut-2-en-1-yl acetate (**7**) in 34% yield. 3-Methyl-4-nitrobut-2-en-1-ol (**8**) was obtained after hydrolysis of **7** with *p*-TsOH in MeOH in 89% yield. Bromination of **8** provided 4-bromo-2-methyl-1-nitrobut-2-ene (**9**) in 97% yield. Treatment of **9** with Et_3N furnished **3** in 98% yield as a 1:3.4 mixture of E/Z-isomers (Scheme 2).



Scheme 2. Synthesis of 1-Nitro-2-methyl-1,3-diene (**3**)

Nitroso acetals were obtained upon heating 1-nitro-2-methyl-1,3-butadiene (**3**) with various alkyl acrylates[6] in the presence of hydroquinone monomethyl ether (MeHQ) and $NaHCO_3$. The nitroso acetal pairs **10a**/**10b**, **11a**/**11b**, and **4a**/**4b** were synthesized from ethyl acrylate in 71% yield, isopropyl acrylate in 74% yield, and methyl acrylate in 81% yield, respectively (Table 1). Because similar endo/exo diastereoselectivity (1:11 dr) was identified in each case, we preferred to use methyl acrylate as the reaction partner because it provided a greater yield and the product isomers could be separated. The 81% isolated yield of the nitroso acetal **4** exceeds the maximum theoretical yield if only the nitrodiene ***Z*-3** had reacted, implying that the nitrodiene **3** underwent E-to-Z isomerization during the period of the cycloaddition. The stereochemistry of the isomers **4a** and **4b** was established through NOESY experiments.

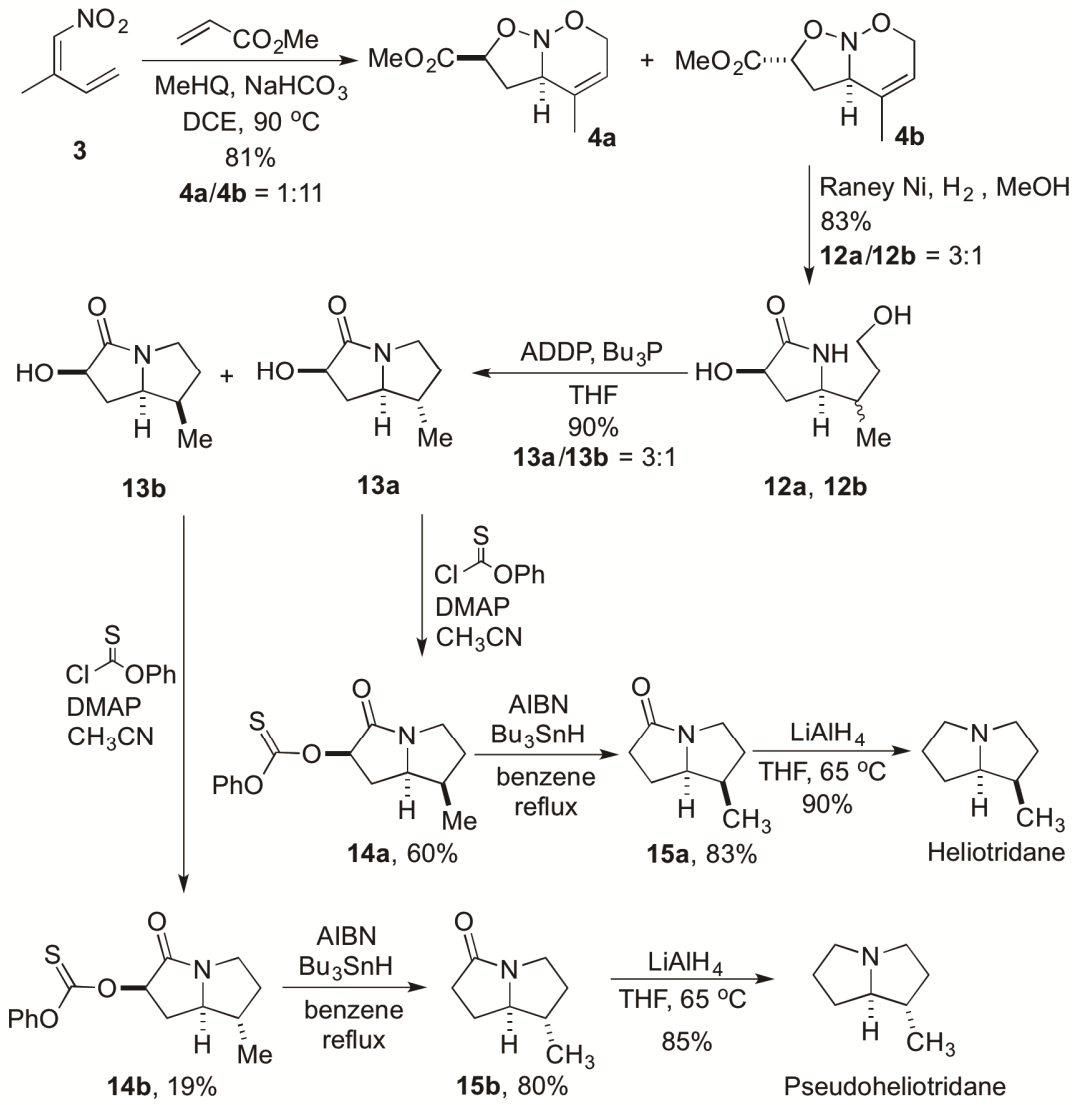
Table 1. Reactions of 1-nitro-2-methyl-1,3-butadiene with dienophiles



3 endo exo

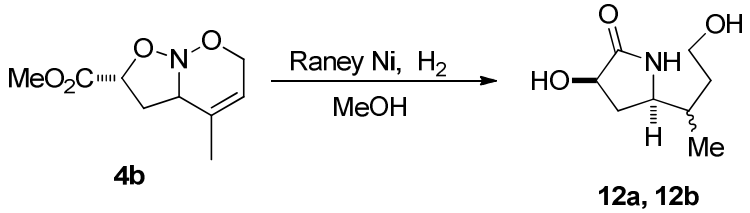
Dienophile	Isomers (endo/exo)	Yield (endo:exo dr)
Methyl acrylate	**4a/4b**	81% (1:11 dr)
Ethyl acrylate	**10a/10b**	71% (1:11 dr)
Isopropyl acrylate	**11a/11b**	74% (1:11 dr)

Hydrogenation of the nitroso acetal **4b** was tested through treatment with Raney nickel in the presence of H_2.[6] Regardless of the H_2 pressure applied in this reaction, we obtained two isomers of the lactam alcohol **12** instead of the desired pyrrolizidinone **5** (Table 2). Because both ring opening and hydrogenation of the double bond occurred in this reaction, the desired pyrrolizidinone **5** or **13** was not obtained, even after heating under reflux in toluene as in our previous study.[6] The hydrogenation of the olefinic bond removed the allylic hydroxyl group and, thereby, prevented the ring closure from occurring while heating in toluene. We obtained the best isomeric ratio of **12a** to **12b** (1:3) under a H_2 pressure of 200 psi (Table 2); these isomers could not be separated.



Scheme 3. Synthesis of Heliotridane and Pseudoheliotridane

Table 2. Hydrogenolysis of **4b**



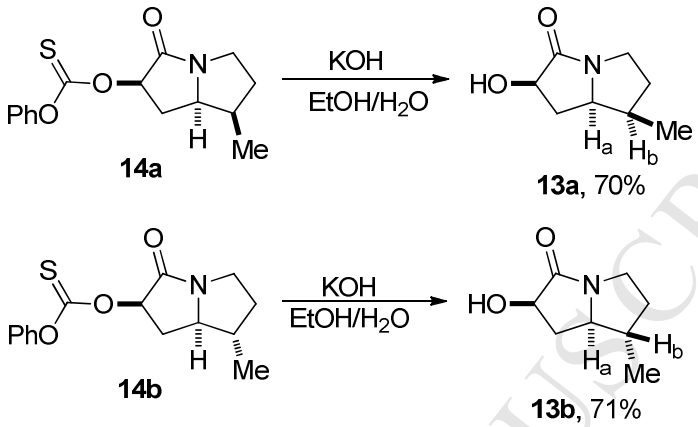
H_2 Pressure	12a:12b Isomer ratio	Product Yield (%)
15 psi (1 atm)	No reaction	0
50 psi	1:1.8	72
100 psi	1:2	78
160 psi	1:1	80
200 psi	1:3	83
450 psi	1:1.5	79

The pyrrolizidinones **13a** and **13b** were obtained in 90% yield through a Mitsunobu reaction of the lactam alcohols **12** in the presence of 1,1´-(azodicarbonyl)dipiperidine (ADDP) and tri-*n*-butylphosphine.[10] Again, these pyrrolizidinones **13a** and **13b** could not be separated.

Treatment of the mixture of compounds **13a** and **13b** with phenyl chlorothionocarbonate in the presence of 4-dimethylaminopyridine (DMAP) afforded the separable thionocarbonates **14a** (60% yield) and **14b** (19% yield). Deprotection of **14a** and **14b**, performed in the presence of more than 4 equiv of KOH under reflux in aqueous EtOH (1:4, v/v) for 1 h, provided pure samples of the pyrrolizidinones **13a** (70% yield) and **13b** (71% yield), respectively (Scheme 4). The stereochemistry of the isomers **13a** and **13b** was established through NOESY experiments. For the pyrrolizidinone **13a**, a strong cross peak appeared between the signals for protons Ha and Hb; for **13b**, no cross peak appeared between the signals of the corresponding protons.

Radical deoxygenations were accomplished by treating the thionocarbonates **14a** and **14b** with 2,2´-azobis(isobutyronitrile) (AIBN) and tributyltin hydride,[10] providing the lactams **15a** and **15b**, respectively, in yields of 83 and 80%, respectively (Scheme 3). Heliotridane was obtained in 90% yield after treatment of the lactam **15a** with LAH; the overall yield of heliotridane from the known nitrodiene **7** was 24%. Similarly, pseudoheliotridane was obtained in 85% yield upon treatment of the lactam **15b**

with LAH; its overall yield from **3** was 7%. The experimental data (melting points; ^{1}H and ^{13}C NMR spectra) of heliotridane and pseudoheliotridane were consistent with those reported in the literature.[11]



Scheme 4. Syntheses of **13a** and **13b**

In summary, the pyrrolizidine alkaloids heliotridane and pseudoheliotridane have been synthesized in six steps, starting with the key step of 6π-electrocyclization/[3+2] dipolar cycloaddition of 1-nitro-2-methyl-1,3-butadiene with methyl acrylate, in overall yields of 24 and 7%, respectively.

Experimental

General Information

All reactions were performed under Ar atmosphere with dry solvents in flame-dried reaction vessels containing stirrer bars. CH_2Cl_2 and 1,2-dichloroethane were distilled afresh from CaH_2; MeOH was distilled afresh from Mg(0); THF and diethyl ether were distilled from Na with benzophenone indicator. All reagents were obtained commercially and used without further purification. Thin layer chromatography (TLC) was performed on 0.25-mm Silicycle Glass-Backed Extra-Hard-Layer, 60-Å silica gel plates (TLG-R10011B-323) and visualized under UV light or through permanganate and anisaldehyde staining. Flash column chromatography was performed using Silicycle SilicaFlash® P60

(230–400 mesh, R12030B) and compressed air. Melting points (mp) were recorded using an Electrothermal capillary melting point apparatus; they are uncorrected. IR spectra were recorded using a Thermo Nicolet Avatar 370 FT-IR spectrometer. NMR spectra were recorded using Bruker ARX-400 and AV-300 instruments calibrated to $CH(D)Cl_3$ as an internal reference (7.26 and 77.00 ppm for ^1H and ^{13}C NMR spectra, respectively). Data for ^1H NMR spectra are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ, ppm). The following abbreviations are used to denote the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet. Mass spectra were recorded using a Waters LCT Premier XE Time-of-Flight instrument controlled by MassLynx 4.1 software. Samples were infused using direct loop injection from a Waters Acquity UPLC into the Multi Mode Ionization source. The lock mass standard for accurate mass determination was leucine enkephalin (Sigma L9133).

3-Methyl-4-nitro-2-buten-1-yl acetate (7). HNO_3 (48 mL, 0.48 mol, 1.6 equiv) was added dropwise over 45 min to Ac_2O (206 mL, 2.2 mol, 7.2 equiv) with cooling in an ice bath and stirring at 23–25 °C. Isoprene (20 g, 0.30 mol, 1.0 equiv) was added slowly over 1 h at 23–25 °C. After an additional 60 min at this temperature, the reaction was quenched through the addition of ice. The aqueous phase was extracted with CH_2Cl_2 and the combined extracts washed with water. The solvent and some of the excess Ac_2O were removed in vacuo (max. bath temperature: 50 °C). The crude product was purified through flash column chromatography (EtOAc/hexanes, 1:9) to provide a colorless oil (34%). IR (ν, cm^{-1}): 2924, 1735, 1551, 1431, 1368, 1227, 1025, 963, 607, 546; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.76 (t, *J* = 6.4 Hz, 1H), 4.86 (s, 2H), 4.65 (d, *J* = 6.4 Hz, 2H), 2.05 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 170.8, 130.2, 129.9, 83.2, 60.4, 20.8, 15.2.

4-Nitro-3-methyl-2-butenol (8). *p*-TsOH (0.50 g, 0.0030 mol, 5.0% equiv) was added to a solution of 3-methyl-4-nitro-2-buten-1-yl acetate (10 g, 0.060 mol, 1.0 equiv) in MeOH at room temperature under

an Ar atmosphere and then the resulting solution was stirred overnight. The solvent was evaporated under reduced pressure and the residue purified through flash column chromatography (EtOAc/hexanes, 1:4) to produce a colorless oil (89%). IR (ν, cm^{-1}): 3355, 2919, 1546, 1374, 1312, 1198, 1006, 694, 629, 573; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.82 (t, *J* = 6.4 Hz, 1H), 4.86 (s, 2H), 4.26 (d, *J* = 6.4 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 135.0, 127.8, 83.5, 59.0, 15.0.

1-Bromo-3-methyl-4-nitro-2-butene (9). Ph_3P (30.3 g, 0.12 mol, 1.5 equiv) was added in small portions to a stirred solution of the alcohol **8** (10 g, 0.077 mol, 1.0 equiv) and CBr_4 (31.5 g, 0.095 mol, 1.25 equiv) in dry CH_2Cl_2 (10 mL) at 0 °C. After the mixture had stirred for 15 min, half of the solvent was evaporated under reduced pressure and the remaining solution treated with Et_2O (20 mL) and filtered. The filtrate was concentrated under reduced pressure and the crude product purified through flash column chromatography (EtOAc/hexanes, 1:39) to give a colorless oil (97%). IR (ν, cm^{-1}): 2988, 2870, 1558, 1541, 1394, 1376, 1141, 1066, 669, 649; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.89 (t, *J* = 8.4 Hz, 1H), 4.82 (s, 2H), 3.92 (d, *J* = 8.4 Hz, 2H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 131.2, 131.0, 83.1, 26.0, 14.7.

1-Nitro-2-methyl-1,3-butadiene (3). Et_3N (9.0 mL, 0.06 mol, 1.2 equiv) was added dropwise to a solution of 1-bromo-3-methyl-4-nitro-2-butene (**9)** (10 g, 0.050 mol, 1.0 equiv) in Et_2O at 0 °C. The ammonium salt was filtered off and filtrate washed with dilute HCl and water. The solution was concentrated under reduced pressure to give a yellow oil (98%) that was not subjected to further purification; IR (ν, cm^{-1}): 2988, 1588, 1557, 1509, 1339, 1146, 991, 822, 765, 669; (*Z*-isomer) ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.64 (dd, *J* = 17.6, 10.8 Hz, 1H), 6.90 (s, 1H), 5.80 (d, *J* = 17.6 Hz, 1H), 5.68 (d, *J* = 10.8 Hz, 1H), 2.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ, ppm): 143.39, 134.78, 130.94, 125.41, 17.41; (*E*-isomer) ^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 7.6 (s, 1H), 6.34 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.86 (d, *J* = 17.2 Hz, 1H), 5.63 (d, *J* = 10.8 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ,

ppm): 143.4, 134.8, 130.9, 125.4, 17.4; HRMS (ESI) calcd for $C_5H_7NO_2$ $[M + H]^+$: *m*/*z* 114.0590, found 114.0660.

Nitroso Acetals 4a and 4b. 1-Nitro-2-methyl-1,3-butadiene (**3**), (2.0 g, 0.018 mol, 1.0 equiv) was added via syringe in one portion to a mixture of $NaHCO_3$ (1.81 g, 0.020 mol, 1.2 equiv), MeHQ (0.90 g, 7.0 mmol, 0.40 equiv), distilled dichloroethane, and methyl acrylate (5 mL, 0.05 mol, 3 equiv) and then the reaction vessel was submerged in an oil bath (90 °C) and stirred for 18 h. The solvent was evaporated in vacuo. The residue was loaded directly onto a silica gel column and purified through flash column chromatography (EtOAc/hexanes, 1:9). **4b**: 74% yield; slightly yellow oil; IR (ν, cm^{-1}): 2974, 2879, 1741, 1540, 1508, 1436, 1348, 1290, 1208, 1181, 1070, 1053, 929, 815, 669, 649; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.51–5.49 (m, 1H), 5.09 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.56–4.49 (m, 1H), 4.16–4.10 (m, 1H), 3.77 (s, 3H), 3.71 (t, *J* = 9.2, Hz, 1H), 2.60–2.54 (m, 1H), 2.49–2.41 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 171.0, 130.30, 119.75, 81.06, 70.28, 67.04, 52.53, 34.56, 20.42; HRMS (ESI) calcd for $C_9H_{13}NO_4$ $[M + H]^+$: *m*/*z* 200.0923, found 200.0939. **4a**: 7% yield; slightly yellow oil; IR (ν, cm^{-1}): 2921, 2844, 1748, 1543, 1521, 1417, 1321, 1295, 1214, 1191, 1088, 1053, 931, 812, 671, 649; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.50–5.49 (m, 1H), 4.91–4.87 (m, 1H), 4.54–4.49 (m, 1H), 4.16–4.11 (m, 1H), 3.79 (s, 3H), 3.63 (t, *J* = 9.2, Hz, 1H), 2.76–2.68 (m, 1H), 2.55–2.48 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 171.4, 130.2, 119.7, 81.6, 71.0, 67.2, 52.6, 33.4, 20.4; HRMS (ESI) calcd for $C_9H_{13}NO_4$ $[M + H]^+$: *m*/*z* 200.0923, found 200.0933.

Lactam Alcohol 12. A catalytic amount of MeOH-washed Raney Nickel 2800 (slurry in H_2O; 3 drops) was added to a solution of the nitroso acetal **4b** (1.0 g, 5.0 mmol) in MeOH.[8] The suspension was stirred under H_2 (200 psi) at room temperature for 18 h. The catalyst was filtered off and washed with MeOH. The filtrate was concentrated in vacuo and the residue purified through silica gel column chromatography (MeOH/EtOAc, 1:9) to afford a white solid (83%). IR (ν, cm^{-1}): 3265, 2987, 2901,

1669, 1405, 1394, 1382, 1250, 1115, 1103, 1065, 1016, 738, 669, 649; ^{1}H NMR (400 MHz, *d*-DMSO, δ, ppm): 7.76 (s, 1H, OH), 7.75 (s, 1H, OH) 5.30 (d, *J* = 5.6, Hz, 2H), 4.38–4.32 (m, 2H), 4.01–3.96 (m, 2H), 3.53–3.32 (m, 4H), 3.21–3.16 (m, 2H), 2.30–2.17 (m, 2H), 1.64–1.45 (m, 4H), 1.36–1.29 (m, 2H), 1.17–1.06 (m, 2H), 0.79 (d, *J* = 6.4, Hz, 3H), 0.74 (d, *J* = 6.4, Hz, 3H); ^{13}C NMR (100 MHz, *d*-DMSO, δ, ppm): 177.1, 176.9, 69.3 (2C), 59.1, 59.1, 54.6, 54.1, 35.8, 35.4, 34.8, 34.3, 33.7, 33.6, 15.6, 14.5; HRMS (ESI) calcd for $C_8H_{15}NO_3$ $[M + H]^+$: *m*/*z* 174.1130, found 174.1127.

***O*-(7-Methyl-3-oxohexahydro-1*H*-pyrrolizin-2-yl) *O*-Phenyl Carbonothioates 14a and 14b.** Tri-*n*-butylphosphine (2.0 mL, 8.0 mmol, 1.5 equiv) and ADDP (2.0 g, 8.0 mmol, 1.5 equiv) were added to a solution of the alcohol **12** (1.0 g, 5.0 mmol) in dry THF (5 mL) at 0 °C under an argon atmosphere. The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h. The solvent was evaporated in vacuo and the residue purified through column chromatography (EtOAc/hexanes, 1:1) to give an inseparable mixture of **13a** and **13b** (90%). DMAP (0.60 g, 0.80 mmol, 0.80 equiv) and phenyl chlorothionoformate (0.70 g, 0.80 mmol, 0.80 equiv) were added to a solution of the alcohols **13a** and **13b** (0.90 g, 5.0 mmol, 1.0 equiv) in MeCN. The resulting yellow solution was stirred at room temperature in a foil-covered round-bottom flask for 2.5 h, then additional charges of DMAP (0.60 g, 0.80 mmol, 0.80 equiv) and phenyl chlorothionoformate (0.70 g, 0.80 mmol, 0.80 equiv) were added. The solution was stirred for an additional 2.5 h and then it was concentrated to afford a yellow oil. The residue was purified through silica gel column chromatography (EtOAc/hexanes, 2:3), with recrystallization (EtOAc/hexanes, 3:7) providing **14a** and **14b** as white solids. **14a**: 60% yield; mp 118–120 °C; IR (ν, cm^{-1}): 2973, 2958, 2926, 2900, 1714, 1653, 1488, 1455, 1424, 1286, 1257, 1215, 1076, 771, 758, 687; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.47–7.43 (m, 2H), 7.35–7.31 (m, 1H), 7.19–7.17 (m, 2H), 6.11 (t, *J* = 9.0, Hz, 1H), 3.71–3.64 (m, 1H), 3.40–3.28 (m, 2H), 3.18–3.11 (m, 1H), 2.34–2.31 (m, 1H), 1.92–1.72 (m, 3H), 1.13 (d, *J* = 5.6, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 194.6, 167.6, 153.6, 129.6 (2C), 126.7, 121.9 (2C), 82.1, 63.1, 41.6, 41.2, 34.7, 33.9, 15.3; HRMS (ESI) calcd

for $C_{15}H_{17}NO_3S$ $[M + H]^+$: *m*/*z* 292.1007, found 292.0999. **14b**: 19% yield; mp 80–82 °C; IR (ν, cm^{-1}): 2972, 2958, 2926, 2900, 1713, 1653, 1286, 1257, 1215, 1185, 1077, 771, 758, 687; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.79–7.55 (m, 2H), 7.46–7.43 (m, 1H), 7.32–7.29 (m, 2H), 6. 23 (t, *J* = 9.0, Hz, 1H), 4.07–4.02 (m, 1H), 3.79–3.74 (m, 1H), 3.33–3.28 (m, 1H), 3.00–2.94 (m, 1H), 2.48–2.36 (m, 2H), 2.12–2.06 (m, 1H), 2.04–1.91 (m, 1H), 1.06 (d, *J* = 7.2, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 194.7, 167.8, 153.6, 129.6 (2C), 126.7, 121.9 (2C), 82.2, 59.4, 39.9, 33.8, 32.8, 29.9, 13.9; HRMS (ESI) calcd for $C_{15}H_{17}NO_3S$ $[M + H]^+$: *m*/*z* 292.1007, found 292.1002.

Pyrrolizidinones 13a and 13b. The carbonothioate **14a** (1.0 g, 3.0 mmol, 1.0 equiv) was added to a solution of KOH (0.20 g, 4.0 mmol, 1.2 equiv) in EtOH/water (4:1, 5 mL) and then the mixture was heated under reflux for 1 h. The EtOH was evaporated off under reduced pressure and the remaining aqueous solution was acidified with 6 M HCl and then extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified through flash column chromatography (EtOAc/hexanes, 1:1) to provide **13a** as a colorless oil (70%); IR (ν, cm^{-1}): 3237, 2970, 2900, 1671, 1457, 1438, 1406, 1394, 1312, 1288, 1251, 1228, 755, 731, 669; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.56–4.51 (m, 1H), 3.64 (bs, 1H, OH), 3.48–3.43 (m, 1H), 3.21–3.11 (m, 2H), 2.71–2.65 (m, 1H), 2.19–2.15 (m, 1H), 1.66–1.53 (m, 3H), 0.99 (d, *J* = 6.0, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.1, 73.4, 63.4, 41.2, 41.0, 36.8, 34.8, 15.4; HRMS (ESI) calcd for $C_8H_{13}NO_2$ $[M + H]^+$: *m*/*z* 156.1024, found 156.1030. The pyrrolizidinone **13b** was prepared in a similar manner from **14b**: 71% yield; colorless oil; IR (ν, cm^{-1}): 3229, 2969, 2900, 1671, 1458, 1438, 1312, 1288, 1251, 1228, 1105, 1065, 1050, 755, 669, 647; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.60–4.55 (m, 1H), 3.84–3.79 (m, 1H), 3.57–3.52 (m, 1H), 3.10–3.05 (m, 2H), 2.49–2.42 (m, 1H), 2.28–2.26 (m, 1H), 2.20–2.15 (m, 1H), 1.76–1.68 (m, 2H), 0.88 (d, *J* = 7.2, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 129.1, 73.3, 59.5, 39.8, 34.0, 32.8, 32.7, 13.9; HRMS (ESI) calcd for $C_8H_{13}NO_2$ $[M + H]^+$: *m*/*z* 156.1024, found 156.1030.

7-Methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (15a). A solution of tributyltin hydride (1.3 g, 4.4 mmol, 1.3 equiv) and AIBN (0.90 g, 0.50 mmol, 0.16 equiv) in benzene (10 mL) was added dropwise over 50 min to a solution of the thionocarbonate **14a** (1.0 g, 1.0 mmol, 1.0 equiv) under reflux in benzene (25 mL). The resulting solution was heated under reflux for an additional 2.5 h and then it was concentrated in vacuo. The residue was purified through column chromatography (silica gel with a plug of potassium fluoride at the top of the column; EtOAc/hexane, 1:1, 2:1, 1:0) to give **15a** as a colorless oil (83%); IR (v, cm^{-1}): 2969, 2891, 1670, 1457, 1438, 1312, 1288, 1106, 755; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.47–3.38 (m, 2H), 3.12–3.08 (m, 1H), 2.69–2.65 (m, 1H), 2.42–2.35 (m, 1H), 2.25–2.18 (m, 2H), 1.70–1.56 (m, 3H), 0.99 (d, *J* = 6.0, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.69, 68.21, 40.95, 40.63, 35.57, 34.92, 25.22, 15.33; HRMS (ESI) calcd for $C_8H_{13}NO$ $[M + H]^+$: *m*/*z* 149.1075, found 140.1065. 7-Methyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (**15b**) was prepared in a similar manner from **14b**: 80% yield; colorless oil; IR (v, cm^{-1}): 2968, 2891, 1671, 1458, 1438, 1312, 1288, 1106, 755, 669; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.93–3.90 (m, 1H), 3.44–3.38 (m, 1H), 3.00–2.94 (m, 1H), 2.65–2.58 (m, 1H), 2.39–2.32 (m, 1H), 2.13–2.08 (m, 2H), 1.96–1.91 (m, 1H), 1.81–1.74 (m, 1H), 1.70–1.65 (m, 1H), 0.76 (d, *J* = 7.2, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 175.0, 64.6, 39.4, 35.0, 34.7, 33.0, 20.9, 13.5; HRMS (ESI) calcd for $C_8H_{13}NO$ $[M + H]^+$: *m*/*z* 149.1075, found 140.1078.

Heliotridane (picrate) and Pseudoheliotridane (picrate). LAH (0.54 g, 14.5 mmol, 0.40 equiv) was added directly to a solution of the lactam **15a** (0.50 g, 3.5 mmol, 0.10 equiv) in Et_2O (4.0 mL) in a sealed tube at 0 °C. After stirring at 65 °C for 6.5 h, the mixture was cooled to RT and then $Na_2SO_4 \cdot 10H_2O$ (0.40 mmol) was added slowly. The resulting solution was stirred at RT overnight. The solid material in the vial was filtered off and washed with Et_2O. The solvent was evaporated from the filtrate under a steady stream of N_2. The residue was treated with picric acid and recrystallized (MeOH)

to give heliotridane as its picrate salt (90%); mp 232–234 °C (decomp); IR (ν, cm^{-1}): 2987, 2900, 1633, 1558, 1518, 1490, 1474, 1456, 1394, 1263, 1161, 1075, 1011, 961, 909, 742, 707; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.36 (bs, 1H, OH), 8.76 (s, 2H), 3.94–3.87 (m, 1H), 3.82–3.71 (m, 1H), 3.62–3.54 (m, 1H), 3.00–2.94 (m, 1H), 2.79–2.71 (m, 1H), 2.19–2.06 (m, 3H), 2.02–1.74 (m, 4H), 1.10 (d, *J* = 6.4, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 162.4, 141.7, 128.2, 126.6 (3C), 74.0, 55.6, 55.4, 40.0, 33.9, 29.3, 24.8, 16.7; HRMS (ESI) calcd for $C_8H_{15}N$ $[M + H]^+$: *m*/*z* 126.1283, found 126.1290. Pseudoheliotridane (picrate) was prepared in a similar manner from **15b**: 90% yield; mp 238–240 °C (decomp); IR (ν, cm^{-1}): 2988, 2910, 2744, 1633, 1558, 1507, 1474, 1456, 1434, 1364, 1312, 1075, 909, 707; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.42 (bs, 1H), 8.88 (s, 2H), 4.34–4.26 (m, 1H), 4.09–4.04 (m, 1H), 3.75–3.66 (m, 1H), 3.16–3.09 (m, 1H), 2.86–2.78 (m, 1H), 2.71–2.59 (m, 1H), 2.22–2.06 (m, 4H), 1.82–1.71 (m, 2H), 1.16 (d, *J* = 6.8, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 162.4, 141.7, 128.2, 126.6 (2C), 118.1, 71.1, 57.0, 54.8, 34.8, 30.7, 26.0, 25.9, 13.5; HRMS (ESI) calcd for $C_8H_{15}N$ $[M + H]^+$: *m*/*z* 126.1283, found 126.1287.

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Notes

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