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Daniel P. Harrison

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Casey H. Richart

Ralph Saporito

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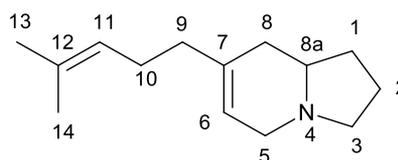


Article Recommendations



Supporting Information

Gosodesmus claremontus



ABSTRACT: Millipedes (Diplopoda) are well known for their toxic or repellent defensive secretions. Here we describe gosodesmine (**1**), 7-(4-methylpent-3-en-1-yl)-1,2,3,5,8,8a-hexahydroindolizine, a unique alkaloid with some terpene character found in the chemical defense secretions of the millipede *Gosodesmus claremontus* Chamberlin (Colobognatha, Platydesmida, Andrognathidae). The structure of **1** was suggested by its mass spectra and GC-FTIR spectra and established from its ^1H , ^{13}C , and 2D NMR spectra and 1D NOE studies. The 7-substituted indolizidine carbon skeleton of **1** was confirmed by unambiguous synthesis. This is the first report of an alkaloid from a platydesmid millipede and the first report of a 7-substituted indolizidine from an arthropod.

Millipedes are the earliest known fully terrestrial animal group and the oldest known terrestrial organisms with chemical defenses. Millipedes synthesize a diversity of defensive chemicals, including benzoquinones, benzaldehydes, HCN, and alkaloids, which are exuded from a series of bilaterally paired openings called ozopores that run laterally along the length of the body.¹ When used in defense against predation, these defensive secretions can ooze out in droplets, flow passively across the cuticle, or be ejected as a stream or spray.¹ The toxicity of these chemicals in some species can blind chickens and kill lizards.^{2,3} The chemical defenses present in millipedes were the subject of a recent review, and research describing the diversity of chemicals in this group of animals continues to receive important attention.^{1,4,5} Here we describe gosodesmine (**1**), a novel alkaloid with some terpene character found in the chemical defense secretions of the millipede *Gosodesmus claremontus* Chamberlin (Colobognatha, Platydesmida, Andrognathidae).

G. claremontus are long slender pinkish millipedes typically found in presocial clusters on woody debris on the floor of California forests. These pink colors are perhaps aposematic—signaling their volatile chemical defenses to potential predators—although this hypothesis needs formal testing.^{1,6} In *Gosodesmus*, defensive chemicals are secreted from ozopores located on the lateral margins of the paranota, from the fifth to the penultimate body segment. *Gosodesmus* aggregate into presocial clusters that include overlapping generations.⁷ These

aggregations may act to increase effectiveness of the presumed aposematic signal, as well as lower the cost of producing defenses by individual millipedes, while affording protection to all members of an aggregation.⁶ Further, first and second stadia platydesmids do not appear to produce defensive secretions,⁶ and therefore a multigenerational cluster likely provides an advantage to the youngest broods.

RESULTS AND DISCUSSION

Initial examination of the MeOH extracts of five collections of *G. claremontus* revealed the presence of a single-nitrogen-containing compound, gosodesmine (**1**), showing a high-resolution molecular ion $[M^+]$ at m/z 205.18307 indicative of the molecular formula $\text{C}_{14}\text{H}_{23}\text{N}$, corresponding to four indices of hydrogen deficiency. A microhydrogenation reaction gave two isomeric products, **2**, in a 10:1 ratio with $M^+ = 209$, thus indicating that **1** had two rings and two double bonds. Additionally, the base peak in the mass spectrum of **1** appeared at m/z 136, a loss of 69, representing allylic cleavage to an alkene. On the other hand, the base peak in the hydrogenated

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material **2** appeared at m/z 124, indicating a loss of the saturated fragment C_6H_{13} from a bicyclic system with a formula $C_8H_{14}N$. The GC-FTIR spectrum of **1** showed an alkene C–H absorption at 3040 cm^{-1} . Additionally, strong Bohlmann bands at 2791 and 2741 cm^{-1} were absorptions consistent with a trans-fused indolizidine with three C–H bonds antiperiplanar to the lone pair of electrons on nitrogen.⁸ The absorption at 2741 cm^{-1} is not present in the GC-FTIR spectrum of the hydrogenation product **2**. However, it is similar to the absorption at 2751 cm^{-1} reported for a C–H bond antiperiplanar to the lone pair of electrons on nitrogen and also adjacent to a carbon–carbon double bond.⁹

NMR spectra were obtained from a sample of ca. 5 mg of **1** purified from the MeOH extracts of *G. claremontus* (Supporting Information). The ^1H NMR spectrum showed two singlets at δ_{H} 1.59 and 1.67 from methyl groups on alkene carbons, two alkene protons at δ_{H} 5.4 and 5.10, and three one-proton signals at δ_{H} 3.45, 3.17, and 2.71. The remaining 12 protons appeared as a series of complex multiplets, δ_{H} 1.7–2.4, and a two-proton multiplet at δ_{H} 1.4. In the ^{13}C NMR spectrum (Table 1), 14 resonances were observed and assigned to four sp^2 carbons at δ_{C} 136.8, 131.6, 124.3, and 118.9, indicating the presence of the two double bonds that were saturated in the hydrogenation experiment. Additionally, there

were three sp^3 carbons bonded to N at δ_{C} 60.2, 54.3, and 52.5, indicating a tertiary amine, and seven other sp^3 carbons.

A DEPT experiment showed two methyl groups at δ_{C} 25.8 and 17.8, methine protons on the carbons at δ_{C} 124.3, 118.9, and 60.2, and no protons on the carbons at δ_{C} 136.8 and 131.6, while the remaining seven carbons were found in CH_2 groups. The COSY spectrum of **1** showed long-range coupling of the single proton triplet at δ_{H} 5.1 to the methyl singlets at δ_{H} 1.59 and 1.67 and the multiplet at δ_{H} 2.1. The multiplicity-edited HSQC spectrum correlates the alkene proton at δ_{H} 5.1 to the carbon resonating at δ_{C} 124.3, while both alkene carbons at δ_{C} 124.3 and 131.6 display long-range HMBC coupling to the methyl singlets at δ_{H} 1.59 and 1.67. Additionally, in a 1D NOE experiment irradiation of the methine triplet (i.e., the explicitly drawn proton in Figure 1) at δ_{H} 5.1 revealed its proximity to the methyl singlet at δ_{H} 1.67. Together these spectra indicate the presence of an isopentenyl group, which had been suggested by the loss of 69 in the mass spectrum of **1**.

The loss of C_6H_{13} at m/z 124 in the mass spectrum of **2**, the two methylene and one methine carbon bound to nitrogen in the ^{13}C NMR spectrum of **1**, and the intense Bohlmann bands in the GC-FTIR spectrum of **1** strongly suggested an indolizidine moiety containing an alkene within the bicyclic portion of **1**. This second alkene is also trisubstituted with a single proton at δ_{H} 5.40. The COSY spectrum of **1** shows this alkene proton to be coupled to the two geminally coupled methine signals at δ_{H} 3.45 and 2.71 ($J = 12.5\text{ Hz}$), whose chemical shifts are remarkably similar to those reported for the C-5 methylene in a 6,7-indolizidine enamine at δ_{H} 3.53 and 2.78.¹⁰ The chemical shifts of the carbons connected to the nitrogen at δ_{C} 60.2, 54.3, and 52.5 also correspond very closely to those reported for the analogous carbons in a 1,2,3,5,8,8a-hexahydroindolizidine at δ_{C} 59.9 (C-8a), 53.7 (C-3), and 51.3 (C-5).¹⁰ Also, the multiplicity-edited HSQC spectrum shows that signals at δ_{H} 3.45 and 2.71 correlate to the methylene carbon nitrogen resonating at δ_{C} 52.5. Furthermore, the indolizidine ring rigidity enables one of the geminal methylene protons (located at δ_{H} 3.45) to couple with the remaining alkene carbons at δ_{C} 136.8 and 118.9 HMBC and supports the supposition of an intraindolizidine alkene.

Additionally, a series of 1D NOE difference experiments were performed to identify important through-space interactions throughout the structure of **1**. Most importantly, the two C-5 proton signals at δ_{H} 3.45 and 2.71 were enhanced when the alkene proton at δ_{H} 5.40 was irradiated, along with subtle allylic methylene signals at δ_{H} 1.04–2.1. Correspondingly, irradiation of either of the proton signals at δ_{H} 3.45 or 2.71 enhanced the alkene proton at δ_{H} 5.40.

These data taken together indicate that the structure of gosodesmine, **1**, is 7-(4-methylpent-3-en-1-yl)-1,2,3,5,8,8a-hexahydroindolizidine (Figure 3). Indeed, the chemical shifts of the carbons connected to the nitrogen at δ_{C} 60.2, 54.3, and 52.5 correspond to those reported for the analogous carbons in 7-morpholino-1,2,3,5,8,8a-hexahydroindolizidine, **3**, at δ_{C} 59.9 (C-8a), 53.7 (C-3), and 51.3 (C-5), while the single proton signals at δ_{H} 3.45 and 2.71 ($J = 12.5\text{ Hz}$) of **1** have chemical shifts similar to those reported for the C-5 methylene in the same compound at δ_{H} 3.53 and 2.78.¹⁰

Furthermore, an HSQC-TOCSY experiment was conducted to support this assignment. HSQC-TOCSY data in general are very powerful in that they (1) indicate direct H–C coupling (i.e., HSQC) and (2) indicate spin-coupled networks within a molecule (TOCSY). Here, HSQC-TOCSY independently

Table 1. NMR Data for Gosodesmine (**1**)

no.	δ_{C} , type	δ_{H} mult. (J in Hz) ^f	HMBC	HSQC-TOCSY	NOE
1	30.8, ^{b,e,f} CH ₂	1.96, m ^b	<i>b</i>	<i>b</i>	<i>c</i>
		1.43, m ^b	<i>b</i>		
2	21.4, ^{b,e,f} CH ₂	1.85, m ^b	<i>b</i>		<i>c</i>
		1.73, m ^b			
3a	54.3, CH ₂	3.17, td (6.8, 1.0)	8a, 1, 2	1, 2	<i>c</i>
3b		2.11, m ^b	<i>b</i>		3a
5a	52.5, CH ₂	3.45, d (15.0)	6, 7, 8a	8	3a, 5b, 6
5b		2.71, d (15.0)	none	8	3b, 5a, 6
6	119.0, CH	5.4, br s	5, 8, 9	5, 8	5a, 5b
7	136.8, C				
8	35.8, ^{b,e} CH ₂	2.12, m ^b	<i>b</i>	<i>b</i>	<i>c</i>
		1.98, m ^b	<i>b</i>		
8a	60.2, CH	2.12, m ^b	<i>b</i>	<i>b</i>	<i>c</i>
9	37.2, ^{b,e} CH ₂	2.08, m ^b	<i>b</i>	<i>b</i>	<i>c</i>
		1.99, m ^b	<i>b</i>	<i>b</i>	<i>c</i>
10	26.4, ^{b,e} CH ₂	2.08, m ^b	<i>b</i>	<i>b</i>	<i>c</i>
11	124.3, CH	5.11, t (8.1)	8, 9, 5	9, 10	13
12	131.6, C				
13	25.8, CH ₃	1.67, s	11, 12, 14	<i>b</i>	<i>c</i>
14	17.8, CH ₃	1.59, s	11, 12, 13	<i>b</i>	<i>c</i>

^aDirect H–C coupling was assigned by multiplicity edited HSQC. ^bAssignment complicated due to overlapping proton resonances. ^cNot attempted due to multiple overlapping proton resonances. ^dExtracted from broad signals in ^1H NMR by NOE signal enhancement by irradiation at 5.4 ppm. ^eIdentified by HSQC-TOCSY or HMBC correlations. ^fH-1 and H-2 signals were difficult to differentiate although methylenes near bridgehead carbons are more deshielded.

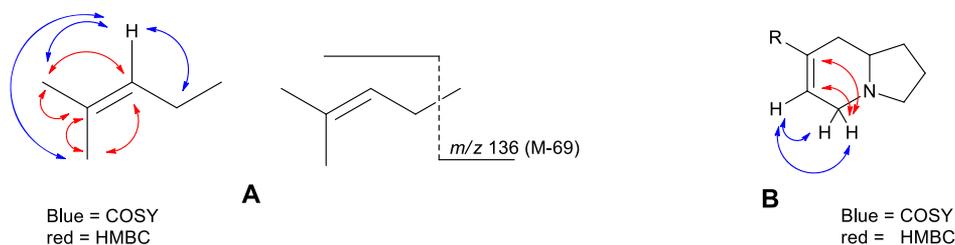


Figure 1. (A) Isopentenyl group of 1. (B) COSY and HMBC connections of the ring alkene of 1.

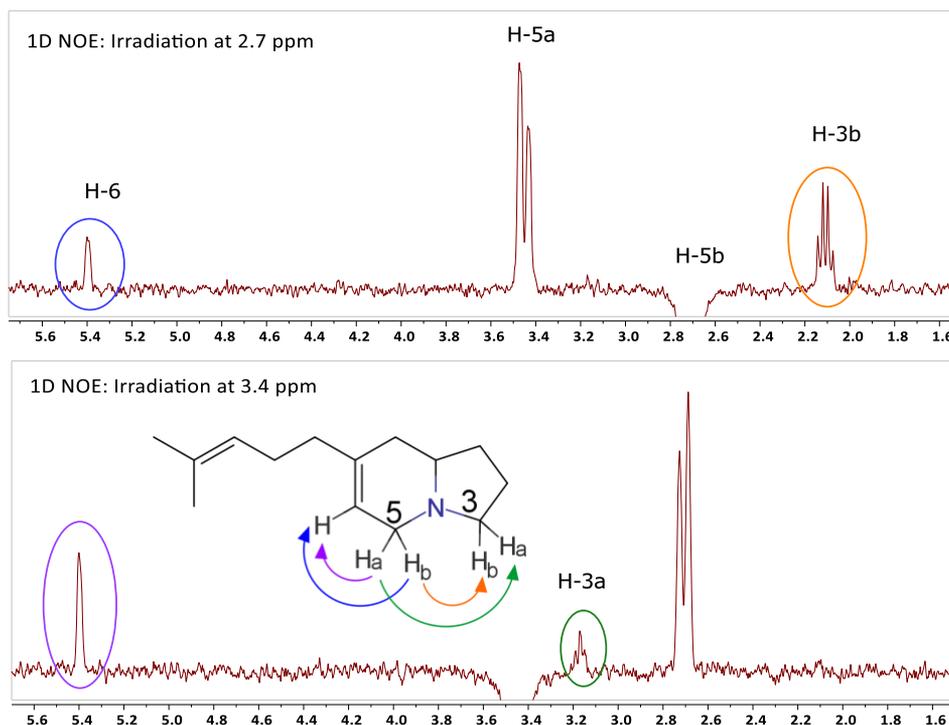


Figure 2. 1D NOE difference spectra for select irradiated protons. Colored ovals around select enhancements correspond to the colored arrows in the molecular structure. The upper figure shows the enhancement resulting from irradiation of the proton at δ 2.7, and the lower shows the enhancement resulting from irradiation at δ 3.4. Additional 1D NOE difference spectra are presented in the [Supporting Information](#).

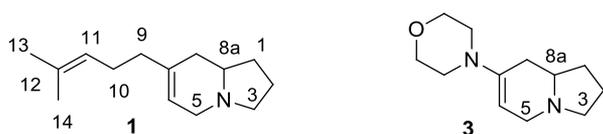


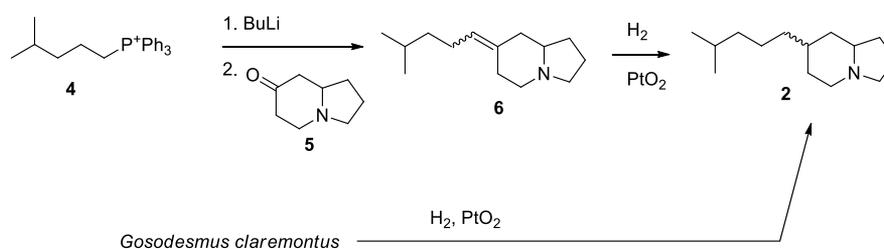
Figure 3. Gosodesmine, 1, and the known enamine 3.

indicates that three unique three-carbon spin-coupled networks are present in gosodesmine (Figure S16). Specifically, the first spin-coupled network is around the five-membered ring, from CH₂-1 to CH₂-3. The second spin-coupled network is around the six-membered ring, CH₂-5 through CH-6 to

CH₂-8. The third spin-coupled network is the isoprenyl moiety. Both of the first two spin-coupled networks show a weak coupling to the CH at the 8a position. These data are consistent with the structure for 1 presented in Figure 3.

Because a literature search revealed no simple 7-substituted indolizidines from natural sources, we also confirmed the carbon–nitrogen skeleton of 1 with the following unambiguous synthesis (Scheme 1). Treatment of 4-methylpentyl triphenylphosphonium bromide 4¹¹ sequentially with *n*-butyllithium and then the known 7-oxoindolizidine 5¹² provided the alkylidene indolizidine 6. Catalytic hydrogenation of a small sample of 6 gave 7-(4-methylpentyl)indolizidine, 2,

Scheme 1. Synthesis of 7-(4-Methylpentyl)indolizidine 2



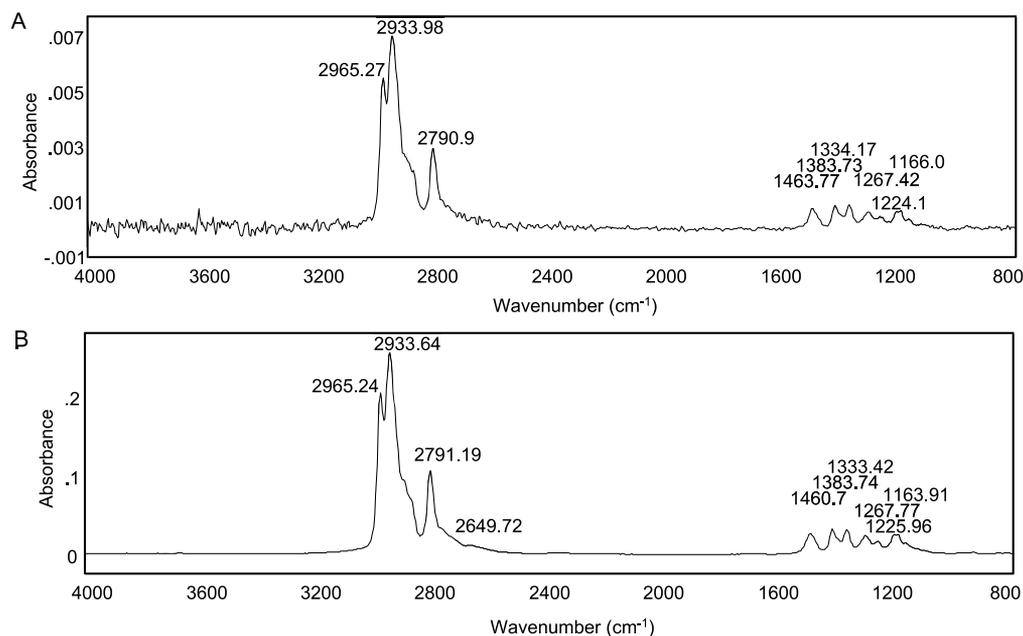


Figure 4. GC-FTIR spectra of **2** from hydrogenation of gosodesmine (A) and **2** synthesized from 7-quinolizidone **5** (B).

as a pair of isomers in a 10:1 ratio whose mass spectra, GC-FTIR spectra (Figure 4), isomer ratios, and gas chromatographic retention times were identical to those of **2** obtained by hydrogenation of natural gosodesmine.

It is quite likely that gosodesmine, **1**, serves as a defensive compound, much like other alkaloids found in millipedes.¹ While other alkaloids with terpene character such as polyzonimine, nitropolyzonamine, and buzonamine have been described from millipedes in the order Polyzoniida,^{13–15} **1** is the first alkaloid to be elucidated from millipedes in the anciently related order Platydesmida.⁵ The C-7-substituted indolizidine structure of **1** is reminiscent of the (8-desmethyl) norpumiliotoxins, indolizidines substituted only at C-6,¹⁶ and of pumiliotoxins generally, a class of amphibian alkaloids whose molecular pharmacology and toxicity have been investigated extensively.¹⁷ Interestingly, pumiliotoxins have been identified in certain species of oribatid mites and formicine ants.¹⁸ Indeed, our preliminary investigations of other millipede species show that platydesmid millipedes may be a rich source of structurally related alkaloids.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotation was measured at the Department of Chemistry at Virginia Tech using a JASCO P-2000 polarimeter. Vapor phase FT-IR spectra were obtained using a Hewlett-Packard model 5965B detector interfaced with a Hewlett-Packard 5890 gas chromatograph fitted with a DB-5, 30 m × 0.25 mm i.d. column. NMR spectra were determined in CDCl₃ using a JEOL 400 YH NMR spectrometer. GC-MS was carried out in the EI mode using a Shimadzu QP-2010 GC-MS equipped with an RTX-5, 30 m × 0.25 mm i.d. column. The instrument was programmed from 60 to 250 °C at 10°/min. HRMS were obtained by the Mass Spectrometry Laboratory of the School of Chemical Sciences at the University of Illinois–Urbana using a Waters GCT Premier time-of-flight mass spectrometer or a Waters Micromass VG 70-VSE mass spectrometer.

Millipedes. The millipedes sampled for these experiments were collected from large woody debris in forests. Typical collection used soft forceps to move entire colonies of (6–39) individuals into ca. 1 mL of MeOH in 3 mL vials sealed with Teflon-lined caps and Teflon

plumbing tape wrapped around the vial/cap interface. All voucher specimens are deposited in the Virginia Museum of Natural History, Martinsville, VA. CHR 6001: USA: CA: San Luis Obispo Co, Cambria, 35.5541° 121.0911°, elev. 70 m. 31 March 2019. CH Richart, C Lee. *Pinus* forest w/occ *Quercus*; woody debris. ca. 13 individuals <https://www.inaturalist.org/observations/21953265>. CHR 6002: USA: CA: San Luis Obispo Co, Cambria, 35.5541° –121.0911°, elev. 70 m. 31 March 2019. CH Richart, C Lee. *Pinus* forest w/occ *Quercus*; woody debris. ca. 9 individuals, <https://www.inaturalist.org/observations/21953284>. CHR 6003: USA: CA: Monterey Co, CA-1 0.4 mi N of Clear Ridge Rd at Captain Cooper Elementary School, 36.2728° 121.8164°, elev. 34 m. 31 March 2019. C Lee. *Quercus* forest; woody debris. ca. 39 individuals. CHR 6004: USA: CA: Monterey Co, CA-1 2.0 mi S of Clear Ridge Rd, 36.2527° 121.7891°, elev. 82 m. 1 April 2019. CH Richart. *Sequoia sempervirens* forest, woody debris. ca. 35 individuals, <https://www.inaturalist.org/observations/21953184>. CHR 6005: USA: CA: Monterey Co, CA-1 2.0 mi S of Clear Ridge Rd, 36.2527° 121.7891°, elev. 82 m. 1 April 2019. CH Richart. *Sequoia sempervirens* forest, woody debris. ca. 6 individuals, <https://www.inaturalist.org/observations/21953203>.

Extraction and Isolation. GC/MS analysis of each of the collections revealed the presence of a single alkaloid. The combined methanol extracts of all five collections were acidified with a small amount of 1% HCl, and the solvent was removed under reduced pressure. The residue was taken up in 2 mL of H₂O and extracted twice with freshly distilled diethyl ether. The aqueous layer was made basic with an excess of K₂CO₃ and extracted twice with freshly distilled diethyl ether. Removal of the solvent from these extracts provided ca. 5 mg of **1**.

Gosodesmine (1): colorless oil; [α]_D²⁶ –3.6 (c 0.225 MeOH); retention index 1586; FTIR ν_{\max} (cm⁻¹) 3040, 2971, 2917, 2791, 2742, 1451, 1383, 1225, 1171, 997; ¹H and ¹³C NMR data, Table 1; HREIMS m/z 205.18307 [M⁺] (calcd for C₁₄H₂₃N, 205.18305).

Catalytic Hydrogenation. A slow stream of hydrogen was bubbled through a 0.2 mL sample of one of the original MeOH extracts of *G. claremontus* containing a few milligrams of PtO₂ for ca. 2 min until the catalyst turned black. GC/MS analysis of the supernatant MeOH showed the absence of **1** and the presence of two products in a 10:1 ratio with identical mass spectra: MS m/z (rel %) 209 (40), 208 (100), 194 (13), 180 (10), 166 (25), 152 (10), 138 (20), 124 (90), 96 (70), 83 (35).

7-(4-Methylpentyl)octahydroindolizidine (2). A 1.6 M solution of *n*-butyllithium in hexane (1.1 mL) was added dropwise to a

slurry containing 0.64 g (1.5 mmol) of 4-methylpentyltriphenylphosphonium bromide (4)¹¹ in 10 mL of THF under argon and was cooled to 0 °C. The mixture was stirred for 0.5 h followed by the dropwise addition of 0.21 g (1.5 mmol) of 7-oxooctahydroindolizidine (5)¹² in 2 mL of anhydrous ether and allowed to come to room temperature overnight. Following the addition of 50 mL of anhydrous ether, the mixture was filtered through Celite, and the solvent removed *in vacuo*. The residue was triturated with 15 mL of anhydrous ether and filtered through a silica gel plug to provide 0.2 g of (*E* and *Z*) 7-(4-methylpentylidene)octahydroindolizidine (6) as a 1:1 mixture of isomers with identical mass spectra: MS *m/z* (rel %) 207 (48, M⁺), 206 (55), 192 (13), 164 (20), 150 (88), 122 (38), 83 (70), 70 (48); HREIMS *m/z* 207.19788 [M⁺] (calcd for C₁₄H₂₅N, 207.19870). A slow stream of hydrogen was bubbled through a solution containing ca. 10 mg of 5 in 1 mL of MeOH containing a few milligrams of PtO₂ for ca. 2 min until the catalyst turned black. GC/MS analysis showed only the presence of two isomers of 2 in a 10:1 ratio having identical mass spectra: MS *m/z* (rel %) 209 (40), 208 (100), 194 (13), 180 (10), 166 (25), 152 (10), 138 (20), 124 (90), 96 (70), 83 (35); HREIMS *m/z* 208.2072 [M - 1⁺] (calcd for C₁₄H₂₆N, 208.2065). See Supporting Information for ¹H and ¹³C NMR spectra. The mass spectra, GC-FTIR spectra (Figure 4), and gas chromatographic retention times of 2 were identical to those of the hydrogenation product from *G. claremontus* by direct comparison and co-injection.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c00722>.

EI mass spectra of 1 and its hydrogenation product 2, GC-FTIR spectra of compound 1, its hydrogenation product 2, and synthetic compound 2; ¹H, ¹³C, 1D NOE, DQF-COSY, TOCSY, HSQC, HSQC-TOCSY, and HMBC NMR of 1; ¹H and ¹³C NMR of 2 (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Tappey H. Jones – Department of Chemistry, Virginia Military Institute, Lexington, Virginia 24450, United States; orcid.org/0000-0001-8807-3017; Phone: 540-464-7422; Email: jonesth@vmi.edu; Fax: 540-464-7261

Authors

Madeline F. Hassler – Department of Chemistry, Virginia Military Institute, Lexington, Virginia 24450, United States; orcid.org/0000-0002-2230-609X

Daniel P. Harrison – Department of Chemistry, Virginia Military Institute, Lexington, Virginia 24450, United States; orcid.org/0000-0003-1840-2561

Casey H. Richart – Santa Barbara Botanic Garden, Santa Barbara, California 93105, United States; orcid.org/0000-0001-7190-7521

Ralph A. Saporito – Department of Biology, John Carroll University, University Heights, Ohio 44118, United States; orcid.org/0000-0003-4762-2774

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c00722>

Notes

The authors declare no competing financial interest.

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