JOC*Note*

Stereoselective Michael Addition of Carbon-, Nitrogen-, Oxygen-, and Sulfur-Centered Nucleophiles on Enantiopure Hydroxylated 6,7-Dehydro-5-oxoindolizidine. Synthesis of Carbon- or Hetero-7-Substituted Swainsonine Analogues

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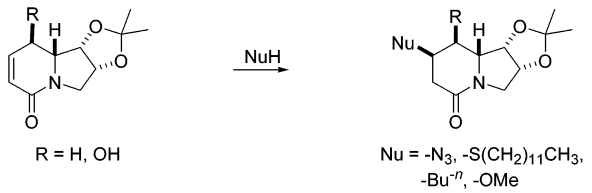

Enantiopure α,β-unsaturated δ-lactams **1** and **2** react stereoselectively with carbon-, nitrogen-, sulfur-, and oxygen-centered nucleophiles. The synthetic potential of these conjugate additions is demonstrated through the synthesis of two new substituted indolizidines: (7*R*)-7-amino-8-deoxyswainsonine **3** and (7*R*)-7-acetylaminoswainsonine **4**.

Polyhydroxylated indolizidines, such as the naturally occurring lentiginosine, swainsonine, and castanospermine, have received broad attention from synthetic organic chemists.[1]

Because of their biological activity, mainly as glycosidase inhibitors,[2] these bicyclic alkaloids are regarded as promising antiviral, antitumor, and immunomodulating agents.[3] As a consequence, a vast literature dealing with their isolation, biological evaluation, and total synthesis is available.[1−3] In an effort to increase selectivity and inhibiting potency, as well as to gain insight on the molecular basis of their activity, several new swainsonine analogues have been synthesized.[1,4] Our work stems from the need of expanding the repertoire of available analogues and presents a novel synthetic strategy to obtain them. Our approach to the total synthesis of this class of hydroxylated indolizidines[5] exploits a ring-closing olefin metathesis (RCM) as a key-step, transforming sugars-derived 2-vinylpyrrolidines (**A**) to hexahydro idolizidine derivative (**B**), Chart 1.

In this paper, we are reporting the results of a study focused on the introduction on C-7 of nitrogen-, sulfur-, oxygen-, and carbon-centered nucleophiles. All these reactions occur by conjugate addition on the carbon−carbon double bond resulting after isomerization of the RCM product and gave with high selectivity derivatives with high stereoselectivity, Chart 1.

The 1,4-addition of nucleophiles to α,β-unsaturated lactams is usually difficult, owing to the electron-donating character of the nitrogen atom.[6a,b] This problem has been solved by the introduction of either a carboalkoxy group on the α-carbon,[7] or a tosyl[6a] or *tert*-butoxycarbonyl[6b] group on the nitrogen atom. There are only a few examples where α,β-unsaturated bicyclo δ-lactam act as good Michael acceptors without necessitating electron withdrawing groups to favor the 1,4-addition.[8] Here we are showing that the unsaturated δ-lactams **1** and **2** undergo straightforward and stereoselective conjugated addition. This observation makes them very interesting intermediates as the objective is that of obtaining a diverse pool of 7-substituted swainsonines and the corresponding 8-deoxyswainsonines. Michael acceptor **1** was obtained by base-induced double bond migration from **5**. This reaction requires rather harsh conditions (DBU at 90 °C) and yields an equilibrium with **1**/**5** ratio of 4.[9] The subsequent conjugate addition can be conducted on isolated and pure **1** but also directly on the equilibrium mixture, Scheme 1.

The unsaturated δ-hydroxylactam **2** was obtained from **5**[5b] as outlined in Scheme 1. Diol **6** was converted to diacetonide derivative **7** and then converted under basic conditions to desired Michael acceptor **2** by β-elimination. The high selectivity in

(1) Reviews: (a) Michael, J. M. *Nat. Prod. Rep.* **2005**, *22*, 603−626. (b) Michael, J. M. *Nat. Prod. Rep.* **2004**, *21*, 625−649. (c) Michael, J. M. *Nat. Prod. Rep.* **2003**, *20*, 458−475. (d) Michael, J. M. *Nat. Prod. Rep.* **2002**, *19*, 719−741. (e) Michael, J. M. *Nat. Prod. Rep.* **2001**, *18*, 520−542. (e) Michael, J. M. *Nat. Prod. Rep.* **2000**, *17*, 579−602.

(2) Gunter, L. In *Iminosugars as Glycosidase Inhibitors*; Stütz, A. E., Ed.; Wiley-VCH: Weiheim, Germany, 1999; pp 31−67 and references therein.

(3) (a) Elbein, A. D.; Molyneux, R. J. In *Iminosugars as Glycosidase Inhibitors*; Stütz, A. E., Ed.; Wiley-VCH: Weiheim, Germany, 1999; pp 216−251 and references therein. (b) Das, P. C.; Robert, J. D.; White, S. L.; Olden, K. *Oncol. Res.* **1995**, *7*, 425−433. (c) Gross, P. E.; Beker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935−944. (d) Elbein, A. D. *FASEB J.* **1991**, *5*, 3055−3063. (e) Cenci di Bello, I.; Fleet, G. W. J.; Namgoomg, S: K.; Todano, K. I.; Winchester, B. G. *Biochem. J.* **1989**, *259*, 855−861. (f) Kino, I.; Inamura, N.; Klakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1985**, *38*, 936−940.

(4) (a) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579−8629. (b) Kadlecikova, K.; Dalla, V.; Marchalin, S.; Decroix, B.; Baren, P. *Tetrahedron* **2005**, *61*, 4743−4754. (c) Fujita, T.; Nagasawa, H.; Uto, Y.; Hashimoto, T.; Asakawa, Y.; Hori, H. *Org. Lett.* **2004**, *6*, 827−830. (d) Cerè, V.; Pollicino, S.; Ricci, A. *J. Org. Chem.* **2003**, *68*, 3311−3314. (e) Diaz-Perez, P.; Garcia-Moreno, M. I.; Mellet, C. O.; Garcia Fernandez, J. M. *Synlett* **2003**, 341−344. (f) Pearson, W. H.; Ron, Y.; Power, J. D. *Heterocycles* **2002**, *58*, 421−430. (g) Pearson, W. H.; Guo, L.; Jewell, T. M. *Tetrahedron Lett.* **2002**, *43*, 2175−2178. (h) Pearson, W. H.; Hembre, E. J. *Tetrahedron Lett.* **2001**, *42*, 8273−8276. (i) Pearson, W. H.; Guo, L. *Tetrahedron Lett.* **2001**, *42*, 8267−8271.

(5) (a) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415−1419. (b) Paolucci, C.; Mattioli, L. *J. Org. Chem.* **2001**, *66*, 4787−4794.

(6) (a) Nagashima, H.; Ozaki, N.; Nashiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657−660. (b) Hagen, T. J. *Synlett* **1990**, 63−66. (c) Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107−1109. (d) The marked minor rate observed in the conjugate addition of metoxide with respect to the thiolate anion makes the thiolate addition a clean addition also in the presence of metoxide in excess.

(7) (a) Amat, M.; Llor, N.; Hidalgo, J.; Hernandez, A.; Bosh, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977−980. (b) Amat, M.; Bosh, J.; Hidalgo, J.; Canto, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, F. J. *J. Org. Chem.* **2000**, *65*, 3074−3084. (c) Amat, M.; Pérez, M.; Llor, N.; Bosh, J.; Lago, E. M.; Molins, E. *Org. Lett.* **2001**, *3*, 611−614. (d) Amat, M.; Pérez, M.; Minaglia, A. T.; Casamitjana, N.; Bosh, J. *Org. Lett.* **2005**, *7*, 3653−3656.

(8) (a) Amat, M.; Pérez, M.; Llor, N.; Bosh, J. *Org. Lett.* **2002**, *4*, 2787−2790. (b) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosh, J. *J. Org. Chem.* **2004**, *69*, 8681−8693. (c) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300−308.

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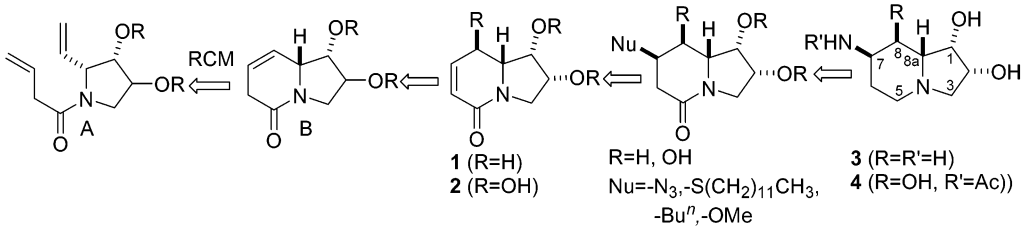
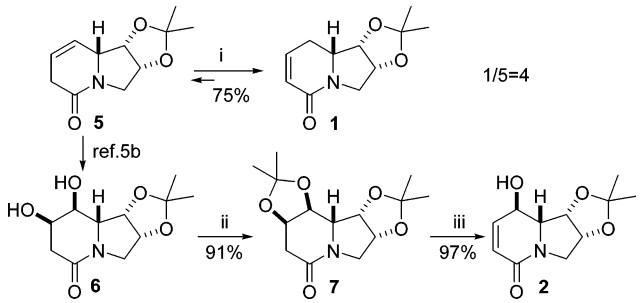
CHART 1



SCHEME 1 [a]



[a] Reagents: (i) DBU (2 equiv), $PhCH_3$, 90 °C, 6 h. (ii) DMP, TsOH (cat), C_6H_6 reflx. (iii) DBU, $PhCH_3$, 90 °C, 5 h.

SCHEME 2

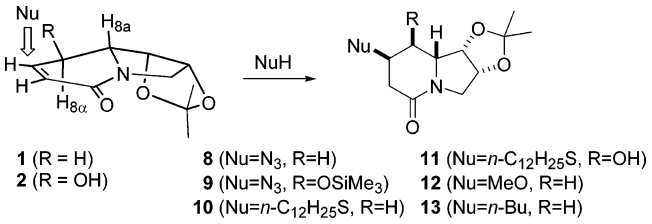


TABLE 1. Nuclephilic Addition on Unsaturated *δ*-Lactam 1 and 2, Scheme 2

substrate	nucleophile	condition	product (yield)
1	Me_3SiN_3[6c]	PhMe, AcOH, DBU, rt	**8** (73%)
2	Me_3SiN_3[6c]	PhMe, AcOH, DBU, rt	**9** (84%)
1	*n*-$C_{12}H_{25}SNa$[6d]	MeOH, rt	**10** (87%)
2	*n*-$C_{12}H_{25}SNa$[6d]	MeOH, rt	**11** (78%)
1	*n*-$Bu_2Cu(CN)Li_2$	Et_2O, −78 to −40 °C	**12** (70%)
1	MeONa	MeOH, rt	**13** (88%)

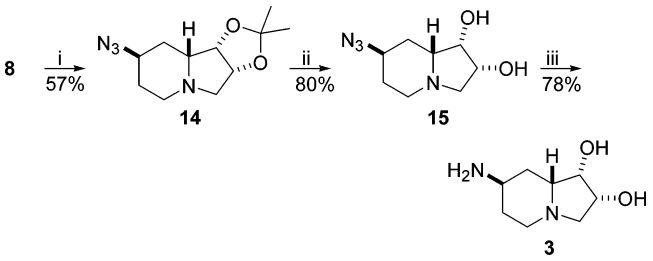
favor of attack on the convex face obtained in the OsO_4-catalized dihydroxylation of **5**[5b] led to stereochemically pure hydroxylated lactam **2**. The Michael addition of nitrogen-, sulfur-, carbon-, and oxygen-centered nucleophiles on lactams **1** and **2**, Scheme 2, takes place under mild condition and in good yields (Table 1).

To the best of our knowledge this is the first example of conjugated addition of heteroatom-centered nucleophiles to α,*β*-unsaturated lactam in the absence of electron withdrawing groups on the nitrogen or on the carbon adjacent to the carbonyl. The sterechemical outcome can be considered as a result of high preference of the nucleophile to attack the convex face,[10,11] antiparallel[12] to $H_{8\alpha}$, of the conformationally rigid lactams (**1** and **2**, Scheme 2). Our hypothesis agrees with previous findings by Amat and co-worker[7a−d,8a,b] where the results of the conjugated addition of carbon-centered nucleophiles on 5-oxo-2,3,8,8a-tetrahydro-5*H*-oxazolo-[3,2-a]pyridine derivatives were similarly justified.[8a,b]

The usefulness of the conjugated addition to compounds **1** and **2** was demonstrated by the synthesis of (7*R*)-7-amino-8-deoxyswainsonine **3**, summarized in Scheme 3, and of (7*R*)-7-acetamidoswainsonine **4**, Scheme 4. In the reduction step (**9**−**16** Scheme 4), the azido group was reduced by $Me_2S{\cdot}BH_3$ [13] to diamine **16** with partial O-desilylation. This is an anomalous behavior, because as showed in Scheme 3 (**8** → **14**) the azido group is stable to the $Me_2S{\cdot}BH_3$.[14]

To obtain the corresponding C-8 epimer of **2**, we attempted the double bond epoxidation of **5** without success.[15]

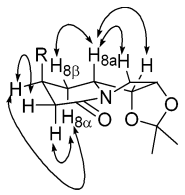
SCHEME 3 [a]



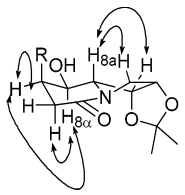
[a] Reagents: (i) (a) Me_2S-BH_3, THF, 18 h, rt. (b) EtOH at −5 °C then reflux for 24 h. (ii) HCl 3 N, 50 °C, 10 h. (iii) H_2−20% $Pd(OH)_2$/C, MeOH.

(9) In a recent paper, it is reported that 8-Me-1,2,3,5,6,8a-hexahydro-5-oxoindolizine (*β*,*γ*-unsaturated *δ*-lactam) is very stable, and conditions could not be found to isomerize the double bond into conjugation with the amide carbonyl group: O'Mahony, G.; Nieuwenhuyzen, M.; Armstrong, P.; Stevenson, P. J. *J. Org. Chem.* **2004**, *69*, 3968−3971.

(10) The stereochemical assignment is based on DPFGSE-NOE: Scott K.; Stonehouse J.; Keeler J.; Hwang L.; Shaka J. *J. Am. Chem. Soc.*, **1995**, *117*, 4199−4200.



Diagnostic DPFGSE-NOE relationships in 8,10,12 and 13



Diagnostic DPFGSE-NOE relationships in 9 and 11

(11) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; p 25−26.

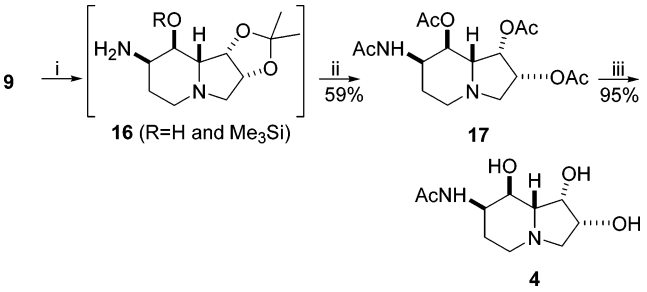
(12) Valls, J.; Toromanoff, E. *Bull. Soc. Chim. Fr.* **1961**, 758−764

(13) Literature reports only one example of azido reduction to amine by means of diborane: Hassner, H.; Levy, L. A. *J. Am. Chem. Soc.* **1965**, *87*, 4203−4204.

(14) (a) Tárraga, A.; Molina, P.; Curiel, D.; Bautiste, D. *Tetrahedron: Asymmetry* **2002**, *13*, 1621−1628. (b) Yadav, J. S.; Thirupathi, P. T.; Hashim, S. R. *Synlett* **2000**, 1049−1051.

(15) Unfortunately, when the unsaturated amide **5** was exposed to epoxidation agents such as *m*-CPBA, dimethyl dioxirane, or peroxyimidic acid,[16] under standard conditions, only unreacted starting material was recovered. Increasing the oxidant amount (more then 5 equiv), reacting for a very long time (days), or using *m*-CPBA/R_2S[17] at 80 °C mainly resulted in substrate degradation.

SCHEME 4 [a]



[a] Reagents: (i) (a) Me_2S-BH_3, THF, 18 h, rt. (b) EtOH at −5 °C then reflux for 24 h. (ii) HCl 3 N, 50 °C, 15 h. (iii) Ac_2O, Py, DMPA cat. (iii) NaOH aq 2 M, MeOH.

In conclusion, this note shows an effective, practical, and highly selective conjugate addition of a variety of nucleophiles on enantiopure 6,7-dehydro-5-oxoindolizidine by which carbon or hetero-7-substituted swainsonine analogues are accessible in a straightforward manner.

Experimental Section

(1*S*,2*R*,8a*R*)-1,2-*O*-Isopropylidene-1,2,3,5,8,8a-hexahydro-5-oxoindolizine, 1. To a stirred solution of **5**[5b] (2.09 g, 10 mmol) in toluene (10 mL), DBU (3.1 g, 20 mmol) was added, and heated under nitrogen at 90 °C. After 6 h, the reaction mixture was cooled at room temperature, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on a column of silica gel (EtOAc) to give the compound **1** (1.56 g, 75%) as colorless solid and recovered unreacted **5** (0.386, 18.5%). Compound **1**: $R_f = 0.2$, with EtOAc; mp 85−86 °C (crystallized from *n*-hexane); $[\alpha]^{22}_D = +128.9$ (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.59 (ddd, $J = 9.9, 6.2, 2.2$ Hz, 1H), 5.89 (ddd, $J = 9.9, 3.2, 0.8$ Hz, 1H), 4.85−4.78 (m, 1H), 4.70 (dd, $J = 6.0, 4.7$ Hz, 1H), 3.99 (d, $J = 13.6$ Hz, 1H), 3.74−3.64 (m, 1H), 3.27 (dd, $J = 13.6, 5.2$, Hz 1H), 2.81−2.67 (m, 1H), 2.41−2.29 (m, 1H), 1.46 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4, 139.4, 124.2, 111.8, 80.6, 78.2, 59.4, 50.3, 26.4, 24.8, 24.2. IR (KBr, cm^{-1}): 1648; Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69; O, 22.94. Found: C, 63.30; H, 7.25; N, 6.67.

(1*S*,2*R*,7*R*,8*S*,8a*R*)-1,2:7,8-Di-*O*-isopropylidene-5-oxoindolizidine, 7. A mixture of diol **6**[5b] (1.95 g, 8 mmol), 2,2-dimethoxypropane (7 mL), and TsOH (76 mg, 0.4 mmol) in dry benzene (35 mL) was refluxed, under nitrogen, with azeotropic removal of water by a Dean−Stark condenser. After 6 h (monitored by TLC with 10% MeOH/EtOAc) the reaction was cooled at room temperature. Then $NaHCO_3$ (128 mg) was added, and the mixture was stirred for 15 min. Solvent evaporation and flash chromatography on a column of silica gel (2% MeOH/Et_2O) gave the diacetonide **7** (2.06 g, 91%) as colorless solid. $R_f = 0.33$, with EtOAc; mp 170−171 °C (crystallized from *n*-hexane); $[\alpha]^{22}_D = -102.2$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.92 (dd, $J = 6.0, 5.3$ Hz, 1H), 4.84 (ddd, $J = 6.0, 5.8, 1.7$ Hz, 1H), 4.60−4.49 (m, 2H), 3.87 (d, $J = 13.6$ Hz, 1H), 3.61−3.55 (m, 1H), 3.41 (dd, $J = 13.6, 5.8$ Hz, 1H), 2.98−2.89 (m,1H), 2.58−2.49 (m, 1H), 1.52 (s, 3H), 1.49 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 112.5, 110.1, 80.0, 77.6, 72.3, 71.7, 61.4, 50.8, 37.0, 27.6, 26.5, 25.2, 24.6. IR (KBr, cm^{-1}): 1656. Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94; O, 28.24. Found: C, 59.54; H, 7.46; N, 4.93.

(1*S*,2*R*,8*R*,8a*R*)-8-Hydroxy-1,2-*O*-isopropylidene-1,2,3,5,8,8a-hexahydro-5-oxoindolizine, 2. Obtained from **7** (1.42 g, 5 mmol) by reaction with DBU according to the procedure described for the preparation of **1**. After 5 h (monitored by TLC with 7% MeOH/CH_2Cl_2), the reaction mixture was cooled and the solvent distilled under reduced pressure. The residue was purified by flash chromatography on a column of silica gel (1% to 7% MeOH/Et_2O) to give the compound **2** (1.09 g, 97%) as a colorless solid. $R_f = 0.3$ with 7% MeOH/CH_2Cl_2; mp 127−128 °C (crystallized from *n*-hexane/EtOAc 5:1, v/v); $[\alpha]^{23}_D = -3.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (dd, $J = 10.1, 1.8$ Hz 1H), 5.83 (dd, $J = 10.1, 2.5$ Hz, 1H), 4.96−4.89 (m,1H), 4.88−4.81 (m, 2H), 3.98 (d, $J = 13.5$ Hz, 1H), 3.64 (dd, $J = 11.4, 3.8$ Hz, 1H), 3.31 (dd, $J = 13.5, 4.2$ Hz, 1H), 3.10 (bs, OH), 1.47 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 145.1, 123.6, 112.1, 79.4, 78.2, 65.9, 65.6, 50.5, 26.3, 24.7. IR (KBr, cm^{-1}): 3343, 1650, 1593. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22; O, 28.41. Found: C, 58.54; H,6.69; N, 6.23.

(1*S*,2*R*,7*S*,8a*R*)-7-Azido-1,2-*O*-isopropylidene-5-oxoindolizidine, 8. To a solution of azidotrimethylsilane (1.32 mL, 10 mmol) dissolved in anhydrous toluene (1 mL), AcOH (0.58 mL, 10 mmol) was added at room temperature and under nitrogen. After stirring for 20 min, the unsaturated lactam **1** (0.209 g, 1 mmol) was added followed by DBU (45 μL, 0.3 mmol), and the mixture was stirred at room temperature. After 42 h the reaction mixture was applied directly to a silica gel plug and flash chromatographed with 2% MeOH/CH_2Cl_2 to afford the azido **8** (184 mg, 73%) as colorless oil. $R_f = 0.35$ with EtOAc; $[\alpha]^{23}_D = +5.8$ (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.79−4.73 (m, 1H), 4.64 (dd, $J = 6.0, 4.1$ Hz, 1H), 4.29−4.23 (m, 1H), 4.21 (d, $J = 13.6$ Hz, 1H), 3.68−3.59 (m, 1H), 3.13 (dd, $J = 13.6, 5.1$ Hz, 1H), 2.63−2.47 (m, 2H), 2.11−2.06 (m, 2H), 1.40 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 111.7, 80.7, 77.5, 56.4, 55.3, 50.2, 35.7, 26.7, 26.3, 24.5. IR (film, cm^{-1}): 2105, 1645; Anal. Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21; O, 19.03. Found: C, 52.51; H, 6.41; N, 22.15.

(1*S*,2*R*,7*R*,8*S*,8a*R*)-7-Azido-1,2-*O*-isopropylidene-8-*O*-trimethylsilyl-5-oxoindolizidine, 9. Obtained from **2** (0.225 g, 1 mmol) according to the procedure above-described for the preparation of **8**. After 48 h the reaction mixture was applied directly to a florisil plug and eluted with EtOAc to give the compound **9** (0.286 g, 84%) as colorless solid. $R_f = 0.42$ with 75% EtOAc/petroleum ether; mp 116−118 °C (crystallized from *n*-hexane); $[\alpha]^{24}_D = -34.3$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77−4.68 (m, 2H), 4.30 (dd, $J = 8.5, 2.7$ Hz, 1H), 4.10 (d, $J = 13.5$ Hz, 1H), 3.97−3.92 (m, 1H), 3.64 (dd, $J = 8.5, 3.6$ Hz, 1H), 3.15 (dd, $J = 13.5, 4.9$ Hz, 1H), 2.61−2.46 (m, 2H), 1.40 (s, 3H), 1.32 (s,3H), 0.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 111.8, 79.4, 77.3, 68.3, 61.7, 61.2, 51.0, 35.3, 26.4, 24.6, 0.0. IR (KBr, cm^{-1}): 2104, 1658. Anal. Calcd for $C_{14}H_{24}N_4O_4Si$: C, 49.39; H, 7.11; N, 16.46; O, 18.80, Si, 8.25. Found: C, 49.23; H, 7.12; N, 16.49.

(1*S*,2*R*,7*S*,8a*R*)-7-Dodecylsulfanyl-1,2-*O*-isopropylidene-5-oxoindolizidine, 10. To a 3 M solution of NaOMe in MeOH (1 mL), 1-dodecanthiol (0.478 mL, 2 mmol) was added under nitrogen, and the resulting mixture stirred for 15 min. The lactam **1** (105 mg, 0.5 mmol) was added, and the reaction maintained at room temperature. After 15 h (monitored by TLC with EtOAc), the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 0.1 M HCl (2 mL) and water, and then dried on $MgSO_4$. The residue, after solvent evaporation, was purified by flash chromatography on a column of silica gel to give the sulfide **10** (179 mg, 87%) as a waxy material. $R_f = 0.30$ with EtOAc/petroleum ether 3:1; $[\alpha]^{21}_D = -5.5$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77−4.71 (m, 1H), 4.63 (dd, $J = 6.0, 4.1$ Hz, 1H), 4.22 (d, $J = 13.5$ Hz, 1H), 3.77−3.68 (m, 1H), 3.46−3.38 (m, 1H), 3.11 (dd, $J = 13.5, 5.0$ Hz, 1H), 2.72 (dd, $J = 17.6, 5.2$, Hz, 1H), 2.58−2.42 (m, 3H), 2.23 (ddd, $J = 17.6, 9.8, 3.5$ Hz, 1H), 2.09−1.99 (m, 1H), 1.64−1.52 (m, 2H), 1.40 (s, 3H), 1.32 (s, 3H), 1.40−1.18 (m, 18H), 0.92−0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 111.7, 81.2, 77.7, 57.2, 50.2, 37.7, 37.2, 31.9, 31.0, 29.6 (2 C's), 29.54, 29.48, 29.46, 29.3, 29.2, 28.9, 27.5, 26.4, 24.6, 22.7, 14.1. IR (KBr, cm^{-1}): 1653. Anal. Calcd for $C_{23}H_{41}NO_3S$: C,

67.11; H, 10.04; N, 3.40; O, 11.66; S, 7.79. Found: C, 67.01; H, 10.07; N, 3.41; S, 7.81.

(1*S*,2*R*,7*R*,8*S*,8a*R*)-7-Dodecylsulfanyl-8-hydroxy-1,2-*O*-isopropylidene-5-oxoindolizidine, 11. Obtained from **2** (113 mg, 0.5 mmol) according to the procedure described above for the preparation of **10**. After 10 h (monitored by TLC with 1.5% MeOH/EtOAc), the reaction mixture was diluted CH_2Cl_2 (10 mL), washed with 0.1 M HCl (2 mL) and water (2 × 2 mL), and then dried on $MgSO_4$. After solvent evaporation, the residue was purified by flash chromatography on a column of silica gel to give the sulfide **11** (167 mg, 78%) as a waxy material. $R_f = 0.3$ with EtOAc. $[\alpha]^{21}_D = -61.0$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.76 (dd, *J* = 6.0, 3.9 Hz, 1H), 4.73 (dd, *J* = 6.0, 4.7 Hz, 1H), 4.33−4.26 (m, 1H), 4.23 (d, *J* = 13.5 Hz, 1H), 3.49 (dd, *J* = 6.0, 4.0 Hz, 1H), 3.36−3.29 (m, 1H), 3.05 (dd, *J* = 13.5, 4.7 Hz, 1H), 2.82 (d, *J* = 6.0 Hz, OH), 2.72−2.52 (m, 4H), 1.66−1.55 (m, 2H), 1.40 (s, 3H), 1.40−1.22 (m, 18H), 1.32 (s, 3H), 0.92−0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 111.9, 79.8, 77.6, 65.2, 63.6, 50.2, 46.2, 35.7, 31.9, 31.6, 29.8, 29.61 (2 C's), 29.56, 29.5, 29.3, 29.2, 28.8, 26.3, 24.4, 22.7, 14.1. IR (KBr, cm^{-1}): 3495, 1650. Anal. Calcd for $C_{23}H_{41}NO_4S$: C, 64.60; H, 9.66; N, 3.28; O, 14.97; S, 7.50. Found: C, 64.79; H, 9.67; N, 3.29; S, 7.48.

(1*S*,2*R*,7*S*,8a*R*)-7-*n*-Butyl-1,2-*O*-isopropylidene-5-oxoindolizidine, 12. The lactam **1** (105 mg, 0.5 mmol) was added to 1 M solution of *n*-$Bu_2Cu(CN)Li_2$[18] in Et_2O (1 mL, 1 mmol) at −78 °C and under nitrogen. The yellow solution was stirred at −78 °C for 1 h and then left to warm spontaneously at 0 °C. After 1 h, the reaction was quenched with saturated aqueous solution of NH_4Cl (0.2 mL) poured at room temperature onto saturated NH_4Cl (2 mL) and stirred for 1 h. The mixture was extracted with Et_2O (2 × 10 mL), and the combined organic phases were washed sequentially with aqueous NH_4Cl (3 mL), water, and brine. After solvent evaporation, the crude was flash chromatographed on a column of silica gel to give the compound **12** (94 mg, 70%) as colorless oil. $R_f = 0.3$ with 3% MeOH/Et_2O; bulb to bulb distilled at 80 °C/1 mm; $[\alpha]^{21}_D = +7.9$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.74−4.67 (m, 1H), 4.58 (dd, *J* = 6.0, 4.1 Hz, 1H), 4.26 (d, *J* = 13.4 Hz, 1H), 3.48−3.38 (m, 1H), 3.02 (dd, *J* = 13.4, 4.9 Hz, 1H), 2.44 (dd, *J* = 16.1, 4.6 Hz, 1H), 2.17−2.01 (m, 3H), 1.80−1.68 (m, 1H), 1.40 (s, 3H), 1.38−1.26 (m, 6H), 1.32 (s, 3H), 0.95−0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 111.6, 81.5, 77.8, 57.5, 49.9, 37.1, 33.5, 31.1, 29.3, 26.8, 26.4, 24.7, 22.7, 14.0. IR (film, cm^{-1}): 1655. Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24; O, 17.95. Found: C, 67.51; H, 9.39; N, 5.22.

(1*S*,2*R*,7*S*,8a*R*)-1,2-*O*-Isopropylidene-7-methoxy-5-oxoindolizidine, 13. The unsaturated lactam **1** (105 mg, 0.5 mmol) was added, under nitrogen, to a 1 M solution of NaOMe in MeOH (0.75 mL, 0.75 mmol) at 0 °C. After 5 min the reaction was left to warm at room temperature and stirred for 24 h (monitored by TLC with EtOAc). Then the reaction was quenched with 1 M HCl (0.75 mL) addition at 0 °C and extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was washed with water (3 mL) and dried over $MgSO_4$. After solvents evaporation under reduced pressure, the crude was purified by flash chromatography on a column of silica gel to give the compound **13** (106 mg, 88%) as colorless solid. $R_f = 0.28$ with EtOAc; mp 89−90 °C (crystallized from *n*-hexane); $[\alpha]^{20}_D = +29.9$ (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.78−4.71 (m,1H), 4.64 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.18 (d, *J* = 13.4 Hz, 1H), 3.90−3.83 (m, 1H), 3.69−3.60 (m, 1H), 3.35 (s, 3H), 3.14 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.61 (d, *J* = 17.6 Hz, 1H), 2.39 (dd, *J* = 17.6, 3.7 Hz, 1H), 2.24−2.13 (m, 1H), 1.98−1.87 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 111.7, 81.0, 77.6, 73.4, 56.2, 56.1, 50.2, 35.7, 26.4 (2 C's), 24.7. IR (film, cm^{-1}): 1658. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81; O, 26.52. Found: C, 59.86; H, 7.92; N, 5.80.

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Supporting Information Available: NMR spectra of new compounds and experimental details for the preparation of **14**, **15**, **3**, **17**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Payne, G. B.; Deming, P. H.; William, P. H. *J. Org. Chem.* **1961**, *26*, 659−663. (b) Bach, R. D.; Knigh, J. W. *Org. Synth.* **1981**, *60*, 63−65.

(17) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64−65.

(18) Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley & Sons: Chichester, U.K., 1994; p 307.