Complementary Use of Iminium Ion and *N*-Acyliminium Ion Cyclization Initiators for Asymmetric Synthesis of Both Enantiomers of Hydroxylated Indolizidines

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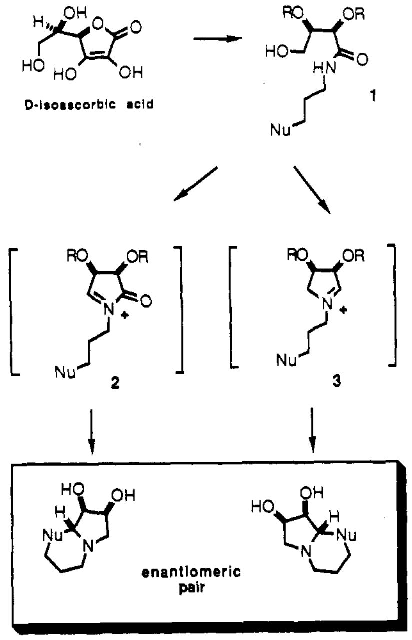
The indolizidinediol 4 and its antipode were prepared by short efficient sequences which diverge from amide 9; the latter intermediate was prepared in three steps from commercially available D-isoascorbic acid. Key steps are (a) $BF_3 \cdot OEt_2$-promoted *N*-acyliminium ion cyclization of 2-acetoxy lactam 11 to form the (1*R*,2*R*,8a*R*)-tetrahydroindolizinone 13, (b) the formation of 2-(ethylthio)pyrrolidine 26, from amide 17, and (c) copper(II) triflate promoted iminium ion cyclization of 26 to afford the (1*S*,2*R*,8a*S*)-tetrahydroindolizine 27.

The need to obtain by synthesis both enantiomers of a compound is a common occurrence in contemporary medicinal chemistry research. In spite of the enormous advances made recently in the area of asymmetric synthesis,[2] classical resolution of the chiral product is often more rapid than parallel asymmetric syntheses of both enantiomers. When enantiodivergence[3] is possible late in a synthesis scheme, the effort involved in preparing both enantiomers can be greatly reduced.

Two basic enantiodivergent synthesis strategies can be visualized. In one an achiral intermediate of appropriate relative configuration is converted into either antipode of a chiral product by use of an enantiotopic group selective transformation.[4,5] This approach is particularly powerful when employed with an advanced intermediate that contains a number of stereogenic centers but is achiral by virtue of a plane of symmetry.[4a,b] A second general strategy employs chiral intermediates that are easily converted into antipodal products. This second mode of enantiodivergence can be realized at either the mechanistic level (in a single step) or at the synthesis strategy level (in several steps). The former is possible when transformations of opposite stereochemical outcome are available. A common example would be the conversion of a simple chiral secondary alcohol into antipodal esters by employing esterification reactions that proceed with formation of either the acyl oxygen (retention) or alkyl oxygen (inversion) bond.[6] Alternatively a chiral intermediate can be converted to enantiomeric products by complementary modifications of two different functional groups.[7,8] This latter strategy is again particularly powerful when realized with an advanced chiral intermediate containing more than one stereogenic center. A new example of this last strategy, which is particularly applicable in the area of alkaloid synthesis, is the subject of this report.

Scheme I



The varied cyclization reactions of iminium ions and related electron-deficient intermediates are among the most useful methods for forming nitrogen heterocycles.[9] We document here a new strategy for preparing both antipodes of hydroxylated indolizidines[10] that features the complementary use of iminium ion and *N*-acyliminium

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[1] (1) NATO Science Fellow and Postdoctoral Fellow de Bourses de Recherche Scientifique de l'OTAN, 1986–1987.

[2] (2) See *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983–1985; Vols. 1–5.

[3] (3) For recent examples of enantiodivergent total syntheses, see: (a) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304. (b) Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035. (c) Takano, S.; Inomata, K.; Kurotaki, A.; Ohkawa, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1987**, *1720*. (d) Prasit, P.; Rokach, J. *J. Org. Chem.* **1988**, *53*, 4422.

[4] (4) Recent examples of chemical enantiotopic group selection, include: (a) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. (b) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 538. (c) Hendrie, S. K.; Leonard, J. *Tetrahedron* **1987**, *43*, 3289. (d) Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, *110*, 6246. (e) Yamashita, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213.

[5] (5) (a) For a review that covers enzymatic enantiotopic group selection, see: Jones, J. B. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 9. (b) See also: Adachi, K.; Kobayashi, S.; Ohno, M. *Chimia* **1986**, *40*, 311. Seebach, D.; Eberle, M. *Ibid.* **1986**, *40*, 315. Jones, J. B.; Jakovac, I. J. *Org. Synth.* **1985**, *63*, 10. Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 2073. Lok, K. P.; Jakovac, I. J.; Jones, J. B. *J. Am. Chem. Soc.* **1985**, *107*, 2521.

[6] (6) For a recent organometallic example of this enantiodivergent synthesis strategy, see Krämer, T.; Hoppe, D. *Tetrahedron Lett.* **1987**, *28*, 5149.

[7] (7) (a) Conversion of (*S*)-(+)-3-hydroxy-2-methylpropanoic acid ("Roche acid") to antipodal four carbon intermediates constitute early examples of this strategy. See e.g.; Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (b) For recent examples, see: Takano, S.; Yanase, M.; Takahashi, M.; Ogasawara, K. *Chem. Lett.* **1987**, *2017* and reference 3d.

[8] (8) Enantiodivergent synthesis strategies are briefly discussed in Nógrádi, M. *Stereoselective Synthesis*; VCH Publishers: Weinheim, 1987; pp 47–48.

[9] (9) For recent reviews, see: (a) Hart, D. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W.; Ed.; Wiley: New York, 1988, Vol. 6, Chapter 3. (b) Heimstra, H.; Speckamp, W. N. *Alkaloids (N.Y.)* **1988**, *32*, 271.

[10] (10) For recent reviews of the chemistry and biology of polyhydroxy indolizidine alkaloids, see: Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W.; Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1. Howard, A. S.; Michael, J. P. *Alkaloids (N.Y.)* **1986**, *28*, 183.

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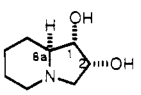
electrophiles.[9,11] The strategy is illustrated in Scheme I and involves preparation of a complementary pair of cyclization initiators, *N*-acyliminium ion **2** and iminium ion **3**, from a common, sugar-derived, amide precursor **1**.[12] We specifically illustrate this approach for the preparation of the (1*S*,2*R*,8a*S*)-indolizidinediol **4** and its antipode.[13]

Indolizidinediol **4** was first obtained from the fungus *Rhizoctonia legumicola*, which also produces the potent biologically active indolizidine alkaloids swainsonine (**5**) and slaframine (**6**).[14] This intermediate, $[\alpha]_D$ −32.5° ($CHCl_3$), has also been isolated recently from spotted locoweed (*A. lentiginosus*).[15] Swainsonine is an inhibitor of certain α-mannosidases and has attracted considerable attention because of its immunostimulatory and possible anticancer properties.[10,16] Harris and co-workers have reported strong evidence that **4** is a late intermediate in the biosynthesis of swainsonine in *R. legumicola*.[17,18] The last stages of the biosynthesis of swainsonine apparently involve epimerization at C-8a as well as oxidation of the piperidine ring.



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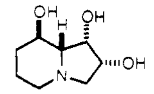

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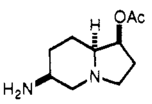

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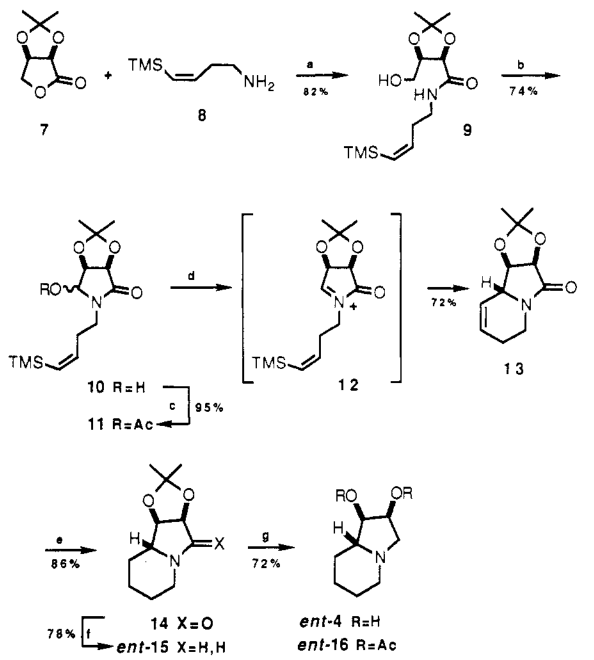
Results

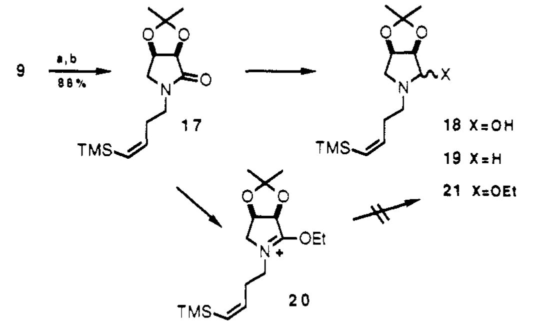
The enantiomerically pure lactone acetonide **7**, available on a large scale in 75% yield from D-isoascorbic acid,[19] provided the starting point for our studies. Aminolysis[20] of **7** with the aluminum amide derivative formed from readily available amine vinylsilane **8**[21,22] and Me_3Al gave amide **9** in 82% yield. Parikh[23] oxidation of this intermediate afforded the desired hydroxy lactam **10** in 74% yield as a 4:1 mixture of stereoisomers. All attempts to cyclize **10** by using standard activating agents (CF_3CO_2H, HCO_2H, CH_3SO_2Cl/Et_3N)[9,22a,c,24] or Lewis acids ($SnCl_4$, Et_2AlCl) were unsuccessful. However, conversion to the acetate derivative **11** followed by cyclization at room temperature with $BF_3{\cdot}OEt_2$ provided the desired tetrahydroindolizinone **13** in 72% yield on a small scale and ca. 50% in larger scale runs.[25] To the limits of detection by 300-MHz ^1H NMR spectroscopy, only a single stereoisomer was formed, consistent with *N*-acyliminium ion **12** undergoing cyclization only from the convex face of this *cis*-bicyclo[3.3.0]octane intermediate.

Scheme II[a]



[a] Conditions: (a) Me_3Al, CH_2Cl_2-hexane, room temperature; (b) Me_2SO, $SO_3{\cdot}py$, room temperature; (c) Ac_2O, DMAP, CH_2Cl_2, −20 °C; (d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temperature; (e) H_2, Pd-C, EtOAc, room temperature; (f) $LiAlH_4$, Et_2O, reflux; (g) 2 M HCl, 80 °C.

Scheme III[a]



[a] Conditions: (a) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C → room temperature; (b) excess NaH, THF, room temperature.

Routine transformations (see Scheme II) converted **13** to *ent*-**4**, $[\alpha]^{23}_D$ +40.2° (*c* 0.88, $CHCl_3$), in 48% yield. Indolizidinediol *ent*-**4** and the diacetate derivative *ent*-**16**, $[\alpha]^{23}_D$ +70.4° (*c* 0.26, $CHCl_3$), exhibited spectroscopic properties (^{13}C NMR, ^1H NMR, IR) identical with those reported[13,14] for the corresponding racemic materials.

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(11) For earlier reports of the use of chiral, nonracemic, *N*-acyliminium ions for enantioselective synthesis of azacyclic products, see, inter alia: Speckamp, W. N.; Wijnberg, B. P. *Tetrahedron Lett.* **1980**, *21*, 1987. Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. Kano, S.; Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1986**, *24*, 621. Hart, D. J.; Yang, T.-K. *Tetrahedron Lett.* **1982**, *23*, 2761.

(12) Chamberlin has recently prepared **2** and *ent*-**2** from ribonolactone and lyxose as well as investigated the preparation of **2** and *ent*-**2** by group-selective reduction of a meso imide: Chamberlin, A. R.; Miller, S. A. to be submitted for publication.

(13) For preparation of this alkaloid in racemic form, see: Colegate, S. M.; Dorling, P. R.; huxtable, C. R. *Aust. J. Chem.* **1984**, *37*, 1503 and ref 12.

(14) Harris, T. M.; Harris, C. M.; Hill, J. E.; ungemach, F. S.; Broquist, H. P.; Wickwire, B. M. *J. Org. Chem.* **1987**, *52*, 3094.

(15) Personal communication from Dr. Russell J. Molyneux, USDA, Western Regional Research Center, Albany, CA. Dr. Molyneux reports that a sample of **4** from *A. lentiginosus* shows the following rotations $[\alpha]_D$ −32.5°, $[\alpha]_{578}$ −33.3°, $[\alpha]_{546}$ −38.6°, $[\alpha]_{436}$ −65.2° ($CHCl_3$).

(16) See, inter alia: Elbein, A. D. *CRC Crit. Rev. Biochem.* **1984**, *16*, 21. Dennis, J. W. *Cancer Res.* **1986**, *46*, 5131. Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Ibid.* **1986**, *46*, 5215. Trugman, G.; Rousset, M.; Zweibaum, A. *FEBS Lett.* **1986**, *195*, 28 and references cited therein.

(17) Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940.

(18) The absolute configuration of **4** has not been rigorously established previously but is inferred to be 1*S*,2*R*,8a*S* because of its efficient biosynthetic conversion to swainsonine.

(19) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth.* **1985**, *63*, 127.

(20) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171.

(21) Available in four steps from 3-butyn-1-ol: Overman, L. E.; Malone, T. C.; McCann, S. F. *Org. Synth.*, in press.

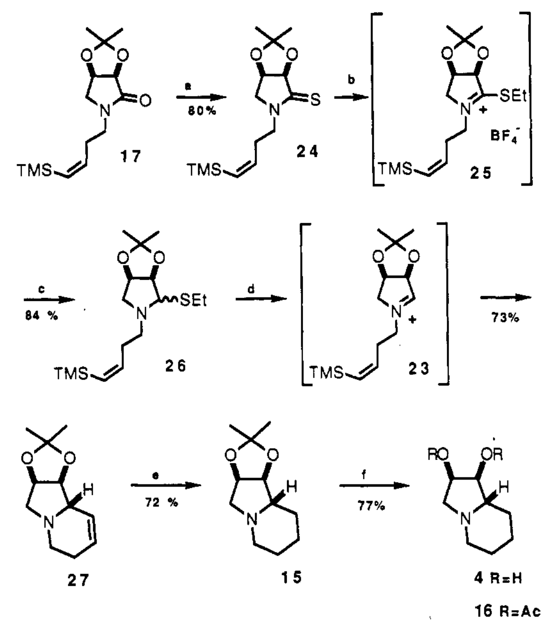
(22) For recent studies and leading references to our earlier investigations of Mannich cyclization reactions of vinylsilanes, see: (a) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (b) McCann, S. F.; Overman, L. E. *Ibid.* **1987**, *109*, 6107. (c) Flann, C.; Overman, L. E. *Ibid.* **1987**, *109*, 6115.

(23) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(24) Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, *23*, 2619.

(25) The yield of **13** from **10** under similar conditions was only 16%.

Scheme IV[a]

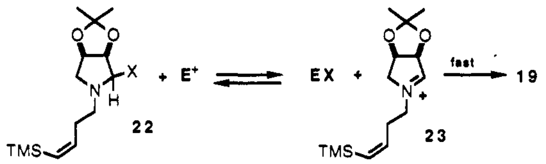


[a] Conditions: (a) $(ArPS_2)_2$, HMPA, 100 °C; (b) Et_3OBF_4, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, room temperature; (c) 1 equiv of $LiBEt_3H$, THF, −78 °C; (d) $Cu(OSO_2CF_3)_2$ THF, reflux; (e) H_2, Pd–C, EtOAc; (f) 2 M HCl, 80 °C.

The successful development of a related sequence for accessing the desired (1*S*,2*R*,8a*S*)-indolizidinediol **4** required considerable experimentation. Lactam **17**, a potential precursor of an iminium ion intermediate (see Scheme I) in the natural enantiomeric series, could be obtained in 88% yield from amide **9** by conversion[26] of the primary alcohol to a mesylate followed by cyclization of this intermediate at room temperature in tetrahydrofuran (THF) in the presence of excess NaH. Attempted direct conversion of **9** → **17** using Mitsunobu conditions[27] was not successful.

We initially examined the controlled reduction of **17** in the hope of obtaining the carbinolamine **18**. In spite of some precedent,[28] including semireduction of 2-pyrrolidones,[29] this conversion could not be satisfactorily accomplished with pyrrolidone **17**, leading always to the formation of unacceptable amounts of the overreduction product pyrrolidine **19**. Attempted selective reduction of the imidate salt **20** to 2-ethoxypyrrolidine **21** using a variety of hydride reducing agents (i-Bu_2AlH, $NaAlH_2(OCH_2CH_2OMe)_2$, $LiAlH(OBu$-$t)_3$, $LiAlH_4$, $LiBEt_3H$, $NaCNBH_3$) was also unsuccessful; significant amounts of pyrrolidine **19** were formed when reactive hydride reductants were employed.

Pyrrolidine **19** must arise from rapid reduction of iminium ion **23** produced in situ by reaction of the initial reduction product **22** (see eq 1) with an electrophilic component of the reaction mixture (e.g. $AlH(OR)_2$ in the reduction of **20** with $NaAlH_2(OR)_2$). Why this ionization is so facile with **22** is not clear, since inductively the acetonide substituent should inhibit formation of cation **23**.



(1)

On the premise that this ionization would be less facile if X were a soft substituent (the electrophiles present in most hydride reducing media are hard), we examined reduction of the thioamide **24**, which was readily available from **17** upon treatment with Lawesson's reagent[30] (Scheme IV). Best success was obtained by conversion of **24** to the thioimidate salt **25**, followed by direct reduction of the latter with 1 equiv of $LiBEt_3H$ at −78 °C in THF.[31] This sequence provided the desired 2-(ethylthio)pyrrolidine **26** in a satisfactory 84% yield from **24**.[32]

Iminium ion-vinylsilane cyclization was readily accomplished by treatment of the α-thio amine **26** with 2 equiv of $Cu(OSO_2CF_3)_2$ in refluxing THF to provide tetrahydroindolizine **27** in 73% yield.[33] As was observed in the cyclization of acyliminium ion **12**, only a *single* stereoisomeric cyclization product was produced. Catalytic hydrogenation of **27** and deprotection[14] of acetonide **15** provided the desired (1*S*,2*R*,8a*S*)-1,2-dihydroxyindolizidine (**4**), $[\alpha]^{22}_D$ −39.4° (*c* 0.58, $CHCl_3$), in 34% yield from **24**. The diacetate derivative **16** exhibited an optical rotation at the sodium D line of −71.9° (*c* 0.54, $CHCl_3$). Thus, the optical rotations of the enantiomeric indolizidinediols **4** and *ent*-**4** and diacetates **16** and *ent*-**16** are identical, within experimental error (±1%), strongly suggesting that both sequences proceeded from **9** with no loss of enantiomeric purity.

Conclusion

Efficient enantiodivergent sequences originating from amide **9** have been developed for the preparation of the levorotatory (1*S*,2*R*,8a*S*)-1,2-dihydroxyindolizidine (**4**) and its antipode. From commercially available D-isoascorbic acid, only nine total steps are required, and the overall yield of both enantiomers is approximately 20%. Since the absolute configuration of D-isoascorbic acid is securely established and the synthesis sequences involve no obvious points for configuration inversion, the negative rotation of the natural indolizidinediol **4** isolated from locoweed[15] confirms the 1*S*,2*R*,8a*S* absolute configuration for this important biosynthetic intermediate.

The investigations recorded here also introduce a more general strategy for asymmetric synthesis of both enantiomers of certain azacyclic targets. In this strategy cyclizations of iminium ion and *N*-acyliminium ion intermediates are employed to form products of opposite absolute configuration. Of potential general utility are the methods described here for selective reduction of an amide to an α-thio amine and for forming an iminium ion from this latter intermediate under mild conditions with copper(II) triflate.

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[26] Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

[27] Mitsunobu, O. *Synthesis* **1981**, 1.

[28] See, inter alia: Bohlmann, F.; Müller, H.-J.; Schumann, D. *Chem. Ber.* **1973**, *106*, 3026. Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324. Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1969**, 877. Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373.

[29] (a) Sanders, E. B.; DeBardeleben, J. F.; Osdene, T. S. *J. Org. Chem.* **1975**, *40*, 2848. (b) Brandänge, S.; Lindblom, L. *Acta Chem. Scand. B* **1979**, *33*, 187.

[30] Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158.

[31] The reduction of amides to amines via thioimidate salts has been reported: Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061. Sundberg, R. J.; Walters, C. P.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 3730.

[32] We were not successful in obtaining this or related intermediates by direct reduction of **17** using the general procedure of Brandänge and Lindblom.[29b]

[33] To the best of our knowledge, Cu(II) salts have not been used previously to generate iminium cations from α-thio amines.

Experimental Section[34]

Preparation of (2*R*,3*R*)-4-Hydroxy-2,3-(isopropylidenedioxy)-*N*-[(*Z*)-4-(trimethylsilyl)-3-butenyl]butanamide (9). $\mathrm{Me_3Al}$ (0.5 mL of a 2M solution in hexane, 1 mmol) was added slowly at room temperature to a solution of amine 8[21] (143 mg, 1 mmol) and $\mathrm{CH_2Cl_2}$ (2 mL). The resulting solution was maintained at room temperature for 15 min, and a solution of lactone 7[19] (158 mg, 1 mmol) in a minimum volume of $\mathrm{CH_2Cl_2}$ (ca. 2 mL) was added.[20] The resulting solution was maintained 1 h at room temperature and then carefully acidified with 1 M HCl to ca. pH 4 and extracted with $\mathrm{CH_2Cl_2}$. The organic extract was dried ($\mathrm{MgSO_4}$) and concentrated. Flash chromatography (silica gel, 1:1 hexane–AcOEt) gave 247 mg (82%) of pure carboxamide **9** as colorless crystals: mp 51–52 °C; $[\alpha]_D$ +32° (*c* 2.5, MeOH); ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$) δ 6.81 (broad s, NH), 6.22 (dt, J = 14.1, 7.2 Hz, $\mathrm{RC}H{=}\mathrm{CHSiR_3}$), 5.67 (d, J = 14.1 Hz, $\mathrm{RCH{=}C}H\mathrm{SiR_3}$), 4.62 (d, J = 7.6 Hz, $\mathrm{C({=}O)C}H\mathrm{OR}$), 4.55 (dt, J = 7.7, 4.1 Hz, $\mathrm{HOCH_2C}H\mathrm{OR}$), 3.78 (dd, J = 11.2, 3.9 Hz, 1 H, $\mathrm{HOC}H_2$), 3.57 (dd, J = 11.2, 8.1 Hz, 1 H, $\mathrm{HOC}H_2$), 3.47–3.30 (m, 2 H, $\mathrm{HNC}H_2$), 2.37 (qd, J = 7.0, 0.9 Hz, $\mathrm{NCH_2C}H_2$), 1.51 (s, 3 H, $\mathrm{CH_3}$), 1.38 (s, 3 H, $\mathrm{CH_3}$), 0.12 (s, 9 H, $\mathrm{SiCH_3}$); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$) 170.7, 144.2, 133.2, 110.1, 77.7, 77.0, 61.8, 38.7, 33.2, 27.1, 24.5, 0.31; IR (KBr) 3373, 3335, 2990, 2957, 2924, 1653, 1530, 1248, 1221, 1079, 1043, 859 cm^{-1}; MS (CI) m/z 302 (MH$^+$), 244, 159; MS (EI) m/z 301 (2), 286 (11), 243 (39), 131 (55), 111 (29), 73 (56), 59 (100). Anal. Calcd for $\mathrm{C_{14}H_{27}O_4NSi}$: C, 55.78; H, 9.03; N, 4.65. Found: C, 55.78; H, 9.07; N, 4.56.

Preparation of (3*R*,4*S*)-1-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-3,4-(isopropylidenedioxy)-5-hydroxypyrrolidin-2-one (10). To a solution of hydroxy amide **9** (60 mg, 0.2 mmol), $\mathrm{Me_2SO}$ (1 mL), and triethylamine (0.2 mL, 1.4 mmol) was added a solution of pyridine–$\mathrm{SO_3}$ complex (95 mg, 0.6 mmol) and $\mathrm{Me_2SO}$ (1 mL).[23] The reaction mixture was stirred for 2 h at room temperature and poured slowly into vigorously stirred ice water (2 mL). The reaction mixture was extracted with $\mathrm{CH_2Cl_2}$ (3 × 20 mL), and the organic extracts were washed with water and brine, dried ($\mathrm{MgSO_4}$), and concentrated. Purification of the residue on silica gel (1:1 hexane–AcOEt) gave 44 mg (74%) of hydroxy lactam **10** (a 4:1 mixture of diastereoisomers by GLC analysis) as a colorless oil. An analytical sample of each isomer was obtained by HPLC (silica gel, 1:0.8 hexane–AcOEt). **Major isomer**: colorless oil; $[\alpha]_D$ −8.3° (*c* 0.79, $\mathrm{CHCl_3}$); ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$) δ 6.24 (dt, J = 14.1, 7.2 Hz, $\mathrm{R_3SiCH{=}C}H\mathrm{R}$), 5.64 (d, J = 14.1 Hz, $\mathrm{R_3SiC}H{=}\mathrm{CHR}$), 5.09 (d, J = 7.7 Hz, $\mathrm{NC}H\mathrm{OH}$), 4.80 (d, J = 5.7 Hz, $\mathrm{C({=}O)C}H\mathrm{OR}$), 4.51 (d, J = 5.7 Hz, $\mathrm{HOCHC}H\mathrm{OR}$), 4.20 (d, J = 7.7 Hz, $\mathrm{O}H$), 3.48 (dt, J = 13.8, 7.6 Hz, 1 H, $\mathrm{R_2NC}H_2$), 3.2, (dt, J = 13.8, 6.9 Hz, 1 H, $\mathrm{R_2NCH_2}$), 2.42 (q, J = 6.9 Hz, $\mathrm{C}H_2\mathrm{CH{=}C}$), 1.39 (s, 3 H, $\mathrm{CH_3}$), 1.36 (s, 3 H, $\mathrm{CH_3}$), 0.12 (s, 9 H, $\mathrm{SiCH_3}$); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$) δ 172.1, 143.9, 132.4, 113.0, 85.0, 79.6, 40.1, 31.0, 27.1, 25.8, 0.06; IR (film) 3322, 2991, 2956, 2898, 1684, 1376, 1248, 1067, 838 cm^{-1}; MS (CI) m/z 300 (MH$^+$), 282; MS (EI) m/z 299.1542 (6, 299.1553 calcd for $\mathrm{C_{14}H_{25}O_4NSi}$), 284 (13), 186 (7), 158 (25), 111(44), 100 (56), 73 (99), 59 (100). **Minor isomer**: colorless crystalline solid; mp 122–123 °C; $[\alpha]_D$ −23.3° (*c* 0.23, $\mathrm{CHCl_3}$); ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$) δ 6.24 (dt, J = 14.3, 7.3 Hz, $\mathrm{R_3SiCH{=}C}H\mathrm{R}$), 5.61 (d, J = 14.1 Hz, $\mathrm{R_3SiC}H{=}\mathrm{CHR}$), 5.10 (dd, J = 11.3, 4.8 Hz, $\mathrm{C}H\mathrm{OH}$), 4.71 (dd, J = 11.0, 6.2 Hz, $\mathrm{HOCHC}H$), 4.67 (d, J = 6.2 Hz, $\mathrm{C({=}O)C}H\mathrm{OR}$), 3.56–3.48 (m, 1 H, $\mathrm{R_2NC}H_2$), 3.46 (d, J = 11.3 Hz, $\mathrm{O}H$), 3.35–3.25 (m, 1 H, $\mathrm{R_2NC}H_2$), 2.50–2.36 (2 H, m, $\mathrm{C}H_2\mathrm{CH{=}C}$), 1.48 (s, 3 H, $\mathrm{CH_3}$), 1.44 (s, 3 H, $\mathrm{CH_3}$), 0.11 (s, 9 H, $\mathrm{SiCH_3}$); IR (KBr) 3425, 2956, 2925, 2850, 1685, 1118, 1085, 862, 837 cm^{-1}; MS (CI) m/z 300 (MH$^+$), 282, 210; MS (EI) m/z 299 (15), 284 (16), 186 (27), 111 (44), 100 (100), 85 (26), 73 (67).

Preparation of (3*R*,4*S*)-1-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-3,4-(isopropylidenedioxy)-5-acetoxypyrrolidin-2-one (11). Acetic anhydride (52 μL, 0.55 mmol) was added to a solution of hydroxy lactam **10** (150 mg, 0.50 mmol), 4-(dimethylamino)pyridine (67 mg, 0.55 mmol), and $\mathrm{CH_2Cl_2}$ at −20 °C. After 15 min the reaction mixture was concentrated, and the residue was purified by flash chromatography (silica gel, 3:2 hexane–EtOAc), giving 163 mg (95%) of acetoxy lactam **11** (a 6:1 mixture of diastereomers by GLC analysis) as a colorless oil. An analytical sample of each isomer was obtained by HPLC (silica gel, 3:2 hexane–AcOEt). **Major diastereoisomer**: colorless oil; $[\alpha]_D$ +14.6° (*c* 0.94, $\mathrm{CHCl_3}$); ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$) δ 6.20 (dt, J = 14.1, 7.2 Hz, $\mathrm{R_3SiCH{=}C}H\mathrm{R}$), 6.07 (s, 1 H, $\mathrm{AcOC}H$), 5.62 (d, J = 14.1 Hz, $\mathrm{R_3SiC}H{=}\mathrm{CHR}$), 4.78 (d, J = 5.7 Hz, $\mathrm{AcOCHC}H\mathrm{OR}$), 4.51 (d, J = 5.7 Hz, $\mathrm{C({=}O)C}H\mathrm{OR}$), 3.64–3.54 (m, 1 H, $\mathrm{{=}CHC}H_2$), 3.15–3.05 (m, 1 H, $\mathrm{{=}CHC}H_2$), 2.46–2.37 (m, 2 H, $\mathrm{R_2NC}H_2$), 2.11 (s, 3 H, $\mathrm{C({=}O)CH_3}$, 1.41 (s, 3 H, $\mathrm{CH_3}$), 1.37 (s, 3 H, $\mathrm{CH_3}$), 0.12 (s, 9 H, $\mathrm{SiCH_3}$); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$) δ 171.9, 169.8, 143.2, 132.4, 113.4, 84.8, 77.2, 76.1, 40.6, 30.8, 26.9, 25.7, 20.8, −0.08; IR (film) 2955, 1728, 1425, 1375, 1249, 1216, 1158, 1106, 1018, 975, 859 cm^{-1}; MS (CI) m/z 342 (MH$^+$), 282, 210, 133, 91, 73; MS (EI) m/z 341.1652 (2, 341.1658 calcd for $\mathrm{C_{16}H_{27}O_5NSi}$), 156 (14), 111 (40), 73 (100), 59 (54). **Minor diastereoisomer** (85% pure by GLC analysis): ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$) δ 6.22 (dt, J = 14.2, 7.0 Hz, $\mathrm{R_3SiCH{=}C}H\mathrm{R}$), 5.98 (d, J = 5.2 Hz, $\mathrm{AcOC}H$), 5.63 (d, J = 14.1 Hz, $\mathrm{R_3SiC}H{=}\mathrm{CHR}$), 4.88 (t, J = 5.9 Hz, $\mathrm{AcOCHC}H\mathrm{OR}$), 4.63 (d, J = 6.1 Hz, $\mathrm{C({=}O)C}H\mathrm{OR}$), 3.64–3.54 (m, 1 H, $\mathrm{{=}CHC}H_2$), 3.20–3.10 (m, 1 H, $\mathrm{{=}CHC}H_2$), 2.53–2.30 (m, 2 H, $\mathrm{R_2NCH_2}$), 2.15 (s, 3 H, $\mathrm{C({=}O)CH_3}$), 1.46 (s, 3 H, $\mathrm{CH_3}$), 1.40 (s, 3 H, $\mathrm{CH_3}$), 0.12 (s, 9 H, $\mathrm{SiCH_3}$); IR (film) 2956, 1724, 1425, 1375, 1249, 1156, 1107, 1053, 1017, 860 cm^{-1}; MS (CI) m/z 342 (MH$^+$), 282, 210, 133, 91, 73.

Preparation of (1*R*,2*R*,8a*R*)-1,2-(Isopropylidenedioxy)-1,5,6,8a-tetrahydro-3(2*H*)-indolizinone (13). To a solution of 11 (50 mg, 0.15 mmol) and $\mathrm{CH_2Cl_2}$ (5 mL) cooled to ca. 0 °C was added freshly distilled $\mathrm{BF_3{\cdot}Et_2O}$ (36 μL, 0.30 mmol). The reaction mixture was allowed to warm to room temperature, and after 4 h the reaction was quenched by adding saturated aqueous $\mathrm{NaHCO_3}$ (5 mL) and extracted with $\mathrm{CH_2Cl_2}$ (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried ($\mathrm{MgSO_4}$), and concentrated. Purification of the residue on silica gel (1:1 hexane–AcOEt) gave 22 mg (72%) of **13** as a pale yellow solid. In larger scale (1.5–3 mmol) runs lower yields (45–55%) were obtained. Recrystallization from hexane gave analytically pure colorless crystals: mp 62–63 °C; $[\alpha]_D$ −68.5° (*c* 1.0, $\mathrm{CHCl_3}$); ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$) δ 5.85–5.77 (m, 2 H, $\mathrm{C}H{=}\mathrm{C}H$), 4.63 (d, J = 6.8 Hz, $\mathrm{C({=}O)C}H\mathrm{OR}$), 4.46 (dd, J = 6.8, 1.7 Hz, $\mathrm{NCHC}H\mathrm{OR}$), 4.25 (dd, J = 13.2, 6.8 Hz, 1 H, eq $\mathrm{C}H\mathrm{NC({=}O)}$), 4.19 (broad s, $\mathrm{NC}H$), 2.98 (ddd, J = 13.2, 11.5, 5.3 Hz, ax $\mathrm{C}H\mathrm{N}$), 2.40–2.20 (m, 1 of $\mathrm{C}H_2\mathrm{CH{=}CH}$), 2.10–1.97 (m, 1 of $\mathrm{C}H_2\mathrm{CH{=}CH}$), 1.49 (s, 3 H, $\mathrm{CH_3}$), 1.39 (s, 3 H, $\mathrm{CH_3}$); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$) δ 169.1, 127.7, 125.7, 113.1, 77.9, 77.2, 61.1, 37.1, 26.7, 25.3, 23.9; IR (KBr) 3040, 2993, 2950, 2915, 2881, 2842, 1702, 1461, 1434, 1390, 1376, 1276, 1232, 1209, 1153, 1090, 1049, 861 cm^{-1}; MS (CI) m/z 210 (MH$^+$); MS (EI) m/z 209 (21), 151 (54), 134 (14), 122 (29), 81 (100), 67 (15), 54 (20). Anal. Calcd for $\mathrm{C_{11}H_{15}O_3N}$: C, 63.13; H, 7.2o; N, 6.69. Found: C, 63.04; H, 7.25; N, 6.63.

Preparation of (1*R*,2*R*,8a*R*)-1,2-(Isopropylidenedioxy)-1,5,6,7,8,8a-hexahydro-3(2*H*)-indolizinone (14). A mixture of **13** (30 mg, 0.143 mmol), 10% Pd on carbon (3 mg), and EtOAc (5 mL) was treated with an excess of $\mathrm{H_2}$ at room temperature. After filtration and concentration, the residue was purified on silica gel (1:1 hexane–AcOEt) to give 26 mg (86%) of **14** as a colorless crystalline solid: mp 107–108 °C; $[\alpha]_D$ −95° (*c* 1.0, $\mathrm{CHCl_3}$); ^{1}H NMR (500 MHz, $\mathrm{CDCl_3}$) δ 4.63 (d, J = 6.6 Hz, $\mathrm{NCHC}H\mathrm{OR}$), 4.35 (d, J = 6.6 Hz, $\mathrm{C({=}O)C}H\mathrm{OR}$), 4.17 (dd, J = 13.2, 5.0 Hz, eq $\mathrm{NC}H$), 3.46 (dd, J = 12.5, 3.0 Hz, $\mathrm{NC}H\mathrm{CHOR}$), 2.71 (td, J = 13.0, 3.4 Hz, ax $\mathrm{NC}H$), 2.0–1.91 (m, 2 H), 1.68 (broad d, J = 13.3 Hz, $\mathrm{C({=}O)NCH_2C}H$), 1.56–1.25 (2 H, m), 1.44 (s, 3 H, $\mathrm{CH_3}$), 1.37 (s, 3 H, $\mathrm{CH_3}$), 1.08 (qd, J = 12.8, 3.5 Hz, $\mathrm{ROCHCHC}H$); ^{13}C NMR (125 MHz, $\mathrm{CDCl_3}$) δ 168.4, 112.6, 77.4, 77.3, 62.1, 40.4, 30.7, 26.7, 25.3, 24.5, 23.7; IR (KBr) 2999, 2971, 2939, 2895, 2859, 1694, 1445, 1435, 1378, 1273, 1210, 1074, 1044, 866 cm^{-1}; MS (CI) m/z 212 (MH$^+$); (EI) m/z 211.1200 (3, 211.1208 calcd for $\mathrm{C_{11}H_{17}O_3N}$), 196 (42), 154 (13), 136 (33), 100 (43), 83 (100), 55 (37). Anal. Calcd for $\mathrm{C_{11}H_{15}O_3N}$: C, 62.52; H, 8.12; N, 6.63. Found: C, 62.46; H, 8.15; N, 6.59.

Preparation of (1*R*,2*R*,8a*R*)-1,2-(Isopropylidenedioxy)indolizidine (*ent*-15). To a suspension of $\mathrm{LiAlH_4}$ (7.2 mg, 0.19 mmol) in ether (2 mL) was added a solution of **14** (10 mg, 0.0474 mmol) and ether (0.5 mL) at room temperature under argon. After

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[34] General experimental details were described recently.[35] GC analyses were done in a temperature-programmed mode using a 12-ft SE-30 quartz capillary column. Optical rotations were measured at room temperature with a Perkin-Elmer 241 MC polarimeter.

[35] Fisher, M. J.; Overman, L. E. *J. Org. Chem.* 1988, *53*, 2630.

heating at reflux for 3 h, the reaction mixture was cooled to room temperature, and the reaction was quenched by adding Rochelle's salt (0.5 mL). After the resulting mixture was stirred for an additional 30 min, the organic layer was separated, washed with brine (3 mL), dried (K_2CO_3), and concentrated. Purification of the residue on silica gel (0.9:1:0.1 hexane–AcOEt–MeOH) gave 7.3 mg (78%) of indolizidine acetonide *ent*-**15** as a colorless oil: $[\alpha]_D$ +51° (*c* 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (m, 1 H, $\mathrm{NCH_2C}H\mathrm{OR}$), 4.19 (t, J = 6.8 Hz, $\mathrm{NCHC}H\mathrm{OR}$), 3.36 (dd, J = 9.8, 6.5 Hz, H-3), 2.96 (broad d, J = 11.4 Hz, H-5 eq), 2.31 (dd, J = 9.5, 5.0 Hz, H-3), 2.14 (td, J = 11.4, 2.8 Hz, H-5 ax), 2.06–1.20 (7 H, m, H-6 eq, H-6 ax, H-7 eq, H-7 ax, H-8 eq, H-8 ax, H-8a), 1.51 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.8, 84.4, 77.4, 68.8, 60.1, 52.5, 28.9, 27.1, 25.1, 24.7, 23.9; IR (film) 2930, 2853, 2803, 2730, 1457, 1372, 1208, 868 cm^{-1}; MS (CI) *m/z* 198 (MH^+), 101, 83, 73; MS (EI, 22 eV) *m/z* 197.1415 (34, 197.1416 calcd for $C_{11}H_{19}O_2N$), 182 (9), 139 (18), 122 (13), 97 (100).

(1*R*,2*S*,8a*R*)-1,2-Dihydroxyindolizidine (*ent*-4). Via the procedure of Harris,[14] acetonide *ent*-**15** (25 mg, 0.127 mmol) was treated with 2 M HCl (5 mL) for 16 h at 80 °C. The solution was evaporated to dryness, and the residue was basified with saturated aqueous KOH (10 mL) and extracted with THF (3 × 20 mL). The organic layer was dried (K_2CO_3) and concentrated. Purification of the residue on silica gel (CH_2Cl_2–5% MeOH) gave 14 mg (72%) of *ent*-**4** as a colorless liquid: $[\alpha]_D$ +40.2°, $[\alpha]_{578}$ +42.4; $[\alpha]_{546}$ +48.9°, $[\alpha]_{436}$ +84.7° (*c* 0.88, $CHCl_3$); ^{1}H NMR (500 MHz) δ 4.21 (q, J = 6.7 Hz, H-2), 3.71 (t, J = 7.7 Hz, H-1), 3.54 (dd, J = 10.3, 6.8 Hz, H-3), 3.06 (broad d, J = 10.9 Hz, H-5 eq), 2.26 (dd, J = 10.3, 5.0 Hz, H-3′), 2.16 (td, J = 11.9, 2.8 Hz, H-5 ax), 2.10–1.24 (m, 7 H, H-6 eq, H-6 ax, H-7 eq, H-7 ax, H-8 eq, H-8 ax, H-8a); ^{13}C NMR (125 MHz, $CDCl_3$) 74.4, 67.7, 66.9, 61.5, 52.8, 28.2, 24.7, 23.5; IR (film) 3375, 2935, 2856, 2808, 2731 cm^{-1}; MS (CI) *m/z* 158 (MH^+); MS (EI) *m/z* 157.1105 (15, 157.1103 calcd. for $C_8H_{15}NO_2$), 140 (8.2), 97 (100), 84 (23), 69 (37), 55 (16). This sample was indistinguishable from natural **4** (isolated from *A. lentiginosus*) by GC analysis.[15]

The diacetate derivative[13] *ent*-**16**, $[\alpha]_D$ +70.4°, $[\alpha]_{578}$ + 67.9°, $[\alpha]_{546}$ +75.2°, $[\alpha]_{436}$ +127° (*c* 0.26, $CHCl_3$) and $[\alpha]_D$ +68.5°, $[\alpha]_{578}$ +70.0°, $[\alpha]_{546}$ +75.9°, $[\alpha]_{436}$ +107° (*c* 0.29, MeOH), showed ^{1}H NMR, ^{13}C NMR, and IR properties consistent with those reported[13,14] for a racemic sample.

Preparation of (3*R*,4*R*)-1-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-3,4-(isopropylidenedioxy)-2-pyrrolidinone (17). To a solution of hydroxy amide **9** (100 mg, 0.332 mmol), Et_3N (47 μL, 0.337 mmol), and CH_2Cl_2 (10 mL) at 0 °C was added $MeSO_2Cl$ (26 μL, 0.336 mmol).[26] After maintaining the reaction for 30 min at 0 °C, hexane (20 mL) was added to precipitate the $Et_3N{\cdot}HCl$ salt, and the reaction mixture was allowed to warm to room temperature. After filtration and concentration, the residue was dissolved in THF (20 mL), and NaH (60% dispersion in mineral oil, 240 mg, 6 mmol) was added slowly with stirring. The resulting mixture was stirred 4 h at room temperature and then cooled to 0 °C, and the reaction was quenched by adding slowly H_2O (10 mL). This mixture was extracted with CH_2Cl_2, and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Chromatographic purification (200–400 mesh silica gel, 1:1 hexane–AcOEt) provided 83 mg (88%) of chromatographically pure pyrrolidinone **17** as colorless crystals: mp 41–42 °C; $[\alpha]_D$ −28° (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (dt, J = 14.0, 7.1 Hz, $\mathrm{R_3SiCH{=}C}H\mathrm{R}$), 5.62 (d, J = 14.1 Hz, $\mathrm{R_3SiC}H\mathrm{{=}CHR}$), 4.71 (t, J = 5.4 Hz, $\mathrm{NCH_2C}H\mathrm{OR}$), 4.64 (d, J = 5.9 Hz, $\mathrm{C({=}O)C}H\mathrm{OR}$), 3.60 (dd, J = 11.4, 4.8 Hz, 1 H of $\mathrm{NC}H_2\mathrm{CHOR}$), 3.46 (d, J = 11.4 Hz, 1 H, of $\mathrm{NC}H_2\mathrm{CHOR}$), 3.41–3.30 (m, 2 H, $\mathrm{C{=}CHC}H_2$), 2.37 (q, J = 7.2 Hz, $\mathrm{R_2NC}H_2$), 1.44 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 0.12 (s, 9 H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.5, 143.9, 132.2, 112.2, 77.6, 72.0, 50.9, 42.3, 30.9, 27.0, 25.6, −0.01; IR (KBr) 2955, 1700, 1374, 1249, 1157, 1103, 859 cm^{-1}; MS (CI) *m/z* 284 (MH^+); MS (EI) *m/z* 283.1598 (40, 283.1603 calcd for $C_{14}H_{25}O_3NSi$), 268 (35), 194 (35), 170 (53), 142 (100), 111 (48), 82 (39), 73 (66), 59 (54). Anal. Calcd for $C_{14}H_{25}O_3NSi$: C, 59.33; H, 8.90; N, 4.94. Found: C, 59.15, H, 8.91; N, 4.89.

Preparation of (3*R*,4*R*)-1-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-3,4-(isopropylidenedioxy)-2-pyrrolidinethione (24). A solution of lactam **17** (28.3 mg, 0.1 mmol), freshly prepared Lawesson's reagent[30] (20.2 mg, 0.05 mmol), and 2 mL of $(Me_2N)_3PO$ was heated at 100 °C for 4 h. The reaction mixture was allowed to cool to room temperature and then poured into water and extracted with ether (4 × 10 mL) until no more thiocarboxamide could be detected (TLC analysis of the aqueous layer). The combined ether phases were dried ($MgSO_4$) and concentrated, and the residue was purified on silica gel (7:3 hexane–AcOEt) to give 24 mg (80%) of thioamide **24** as a yellow oil: $[\alpha]_D$ −81° (*c* 0.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (td, J = 14.3, 7.2 Hz, $\mathrm{R_3SiCH{=}C}H\mathrm{R}$), 5.65 (d, J = 14.0 Hz, $\mathrm{R_3SiC}H\mathrm{{=}CHR}$), 4.91 (d, J = 5.7 Hz, $\mathrm{C({=}S)C}H\mathrm{OR}$), 4.77 (t, J = 5.0 Hz, $\mathrm{NCH_2C}H\mathrm{OR}$), 3.92–3.76 (m, 4 H, $\mathrm{NC}H_2\mathrm{CHOR}$, $\mathrm{C{=}CC}H_2$), 2.57–2.45 (m, 2 H, $\mathrm{R_2NC}H_2$), 1.43 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 0.13 (s, 9 H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 143.1, 132.8, 112.5, 87.6, 73.0, 58.7, 47.6, 29.6, 27.3, 25.9, 0.02; IR (film) 2987, 2954, 1507, 1425, 1311, 1283, 1176, 1048, 859 cm^{-1}; MS (CI) *m/z* 300 (MH^+), 198; MS (EI) *m/z* 299.1367 (4, 299.1375 calcd for $C_{14}H_{25}SiNS$), 198 (100), 111 (57), 73 (72), 59 (54).

Preparation of (3*R*,4*R*)-1-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-3,4-(isopropylidenedioxy)-2-(ethylthio)pyrrolidine (26). To a solution of **24** (25.8 mg, 0.086 mmol) and CH_2Cl_2 (1 mL) was added triethyloxonium tetrafluoroborate (19.6 mg, 0.103 mmol) and 2,6-di-*tert*-butylpyridine (4.6 μL, 0.02 mmol), and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was then concentrated, and the residue was dissolved in dry THF (1 mL). This solution was cooled to −78 °C, and lithium triethylhydroborate (86 μL of a 1 M solution in THF, 0.086 mmol) was added slowly with stirring. After an additional hour at −78 °C, the stirred reaction was quenched by adding a 20% aqueous NaOH (1 mL), and the mixture was allowed to warm to room temperature. The reaction mixture was extracted with CH_2Cl_2, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ solution and brine and dried (K_2CO_3). After filtration and concentration, the crude product was purified by rapid chromatography (200–400 mesh silica gel, 9:0.5:0.5 hexane–AcOEt–Et_3N), giving 24 mg (84%) of thioaminal **26** as a colorless liquid; this intermediate was used immediately in the cyclization step: ^{1}H NMR (300 MHz, C_6D_6) δ 6.43 (td, J = 14.2, 7.2 Hz, $\mathrm{R_3SiCH{=}C}H\mathrm{R}$), 5.65 (d, J = 14.1 Hz, $\mathrm{R_3SiC}H\mathrm{{=}CHR}$), 4.74 (d, J = 6.2 Hz, $\mathrm{EtSCHC}H\mathrm{OR}$), 4.52 (t, J = 5.7 Hz, $\mathrm{NCH_2C}H\mathrm{OR}$), 4.45 (s, 1 H, $\mathrm{C}H\mathrm{SEt}$), 2.97 (d, J = 10.5 Hz, 1 H of $\mathrm{NC}H_2\mathrm{CHOR}$), 2.81–2.72 (m, 1 H), 2.65–2.55 (m, 2 H), 2.40–2.30 (2 H, m), 2.22 (q, J = 7.4 Hz, $\mathrm{SC}H_2$), 1.57 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.05 (t, J = 7.4 Hz, $\mathrm{SCH_2C}H_3$), 0.17 (s, 9 H, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 130.4, 111.8, 86.7, 78.7, 76.6, 57.2, 50.1, 32.2, 26.5, 25.5, 25.0, 15.4, 0.17; IR (film) 2956, 2935, 2818, 1608, 1457, 1379, 1371, 1248, 1209, 1157, 1050, 856 cm^{-1}; MS (CI) *m/z* 330 (MH^+), 284, 210; MS (EI, 70 eV) *m/z* 268 (100), 194 (25), 136 (27), 96 (59), 73 (93), 59 (38); high-resolution MS (EI, 70 eV) 329.1784 (329.1844 calcd for $C_{16}H_{31}O_2SiNS$).

Preparation of (1*S*,2*R*,8a*S*)-1,2-(Isopropylidenedioxy)-1,5,6,8a-tetrahydro-2*H*-indolizine (27). To a solution of copper(II) triflate (61.6 mg, 0.17 mmol) and THF (2 mL) was added a solution of **26** (28 mg, 0.085 mmol) and THF (1 mL), and the resulting mixture was heated at reflux for 6 h. The reaction was then cooled to room temperature, quenched with a saturated solution of $NaHCO_3$, and extracted with ether. The combined organic extracts were washed with brine, dried (K_2CO_3), and concentrated. Chromatography of the residue (200–400 mesh silica gel, 7:2:1 AcOEt–hexane–MeOH) gave 12 mg (73%) of **27** as a colorless liquid: $[\alpha]_D$ −21.7° (*c* 0.515, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85–5.80 (m, 1 H, $\mathrm{CH{=}C}H\mathrm{CH_2}$), 5.59 (d, J = 10.5 Hz, $\mathrm{C}H\mathrm{{=}CHCH_2}$), 4.71 (t, J = 5.4 Hz, $\mathrm{NCH_2C}H\mathrm{OR}$), 4.38 (dd, J = 6.4, 1.9 Hz, $\mathrm{NCHC}H\mathrm{OR}$), 3.59 (broad s, 1 H of $\mathrm{NC}H_2\mathrm{CHOR}$), 3.07 (dd, J = 10.6, 5.1 Hz, 1 H of $\mathrm{NC}H_2\mathrm{CHOR}$), 3.08–3.04 (m, 2 H, $\mathrm{NC}H_2\mathrm{CH_2}$), 2.88 (d, J = 10.6 Hz, 1 H of $\mathrm{NC}H_2\mathrm{CHOR}$), 2.35–2.23 (m, 1 H of $\mathrm{C{=}CC}H_2$), 1.86–1.78 (m, 1 H of $\mathrm{C{=}C\ C}H_2$), 1.56 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3); ^{13}C NMR (125 MZ, $CDCl_3$) δ 127.0, 126.3, 111.6, 83.8, 78.9, 64.5, 54.6, 44.3, 26.5, 24.5, 19.5; IR (film) 3019, 2986, 2928, 2862, 2842, 1381, 1280, 1251, 1180, 996, 911 cm^{-1}; MS (CI) *m/z* 196 (MH^+); MS (EI) *m/z* 195.1248 (11, 195.1259 calcd for $C_{11}H_{17}O_2N$), 136 (11), 120 (13), 95 (100), 81 (27), 67 (17).

Preparation of (1*S*,2*R*,8a*S*)-1,2-(Isopropylidenedioxy)indolizidine (15). By use of a procedure identical with that described for the preparation of **14**, a mixture of **24** (20.9 mg, 0.107 mmol), 10% Pd on carbon (5 mg), and AcOEt (3 mL) was stirred under a H_2 atmosphere for 24 h. Workup followed by purification of the residue by flash chromatography (0.9:1:0.1 hexane–AcOEt–MeOH) gave 15.2 mg (72%) of **15** as a colorless liquid: $[\alpha]_D$ −49.7° (*c* 0.49, $CHCl_3$).

(1*S*,2*R*,8a*S*)-1,2-Dihydroxyindolizidine (4). By use of a procedure identical with that described for the preparation of *ent*-**4**, acetonide **15** (20 mg, 0.101 mmol) was hydrolyzed to give 12.1 mg (77%) of **4** as a colorless liquid: $[\alpha]_D$ −39.4°, $[\alpha]_{578}$ −43.0°, $[\alpha]_{546}$ −52.2°, $[\alpha]_{436}$ −85.1° (*c* 0.58, $CHCl_3$).

The diacetate, prepared as described by Colegate et al.,[13] showed the following optical rotation: $[\alpha]_D$ −71.9°, $[\alpha]_{578}$ −75.0°, $[\alpha]_{546}$ −84.3°, $[\alpha]_{436}$ −145° (*c* 0.54, $CHCl_3$).

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Registry No. **4**, 108866-42-8; *ent*-**4**, 119904-08-4; **7**, 25581-41-3; **8**, 109720-67-4; **9**, 119795-67-4; (5*R*)-**10**, 119795-68-5; (5*S*)-**10**, 119904-05-1; (5*R*)-**11**, 119795-69-6; (5*S*)-**11**, 119904-06-2; **13**, 119795-70-9; **14**, 119795-71-0; **15**, 108796-01-6; *ent*-**15**, 119904-07-3; **16**, 108866-43-9; *ent*-**16**, 119904-09-5; **17**, 119795-72-1; **24**, 119795-73-2; **26**, 119795-74-3; **27**, 119795-75-4.

Reaction of 3-Amino-2-alkenimines with Alkali Metals: Unexpected Synthesis of Substituted 4-(Arylamino)quinolines

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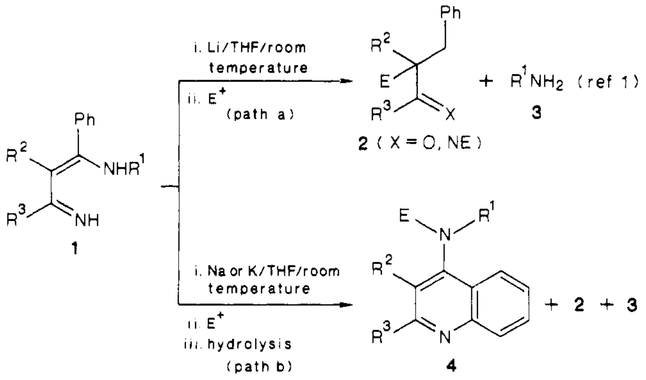
A study of the reduction of 3-amino-2-alkenimines 1 with alkali metals is reported. The nature of the alkali metal plays an important role in the course of the process. In this context, a new and simple method for the regioselective synthesis of 4-(arylamino)quinolines 4 from 1 and sodium or potassium is described.

We have recently described[1] a new synthetic procedure for the regiospecific reduction of 3-amino-2-alkenimine systems 1[2] to saturated monocarbonyl compounds 2. The method consists of the reaction of 1 with lithium in THF at room temperature and later addition of an electrophile (see Scheme I, path a).

In order to explore the generality of the method, we thought to extend this study to other alkali metals such as sodium and potassium, because the initial results[3] indicate that the course of the process was highly influenced by the nature of alkali metal. In this context, we describe here a new, simple, and unexpected method for the regioselective synthesis of substituted 4-(arylamino)quinolines 4 from 1.

The quinoline nucleus is found in many natural products, especially alkaloids.[4] Because of the importance of this ring system, numerous methods have been developed for the synthesis of its derivatives.[4] However, a bibliographical review shows that 4-amino-, and, particularly, 4-(arylamino)quinolines, some of which (e.g., camoquin[5] and its derivatives) show important antimalarial properties, are not easily obtainable.[6-12]

Scheme I



Results and Discussion

The treatment of 3-amino-2-alkenimines 1 with an excess of sodium or potassium at room temperature in an inert solvent such as THF produces intense color changes. After stirring of the mixture during several hours (4–10 h), and addition of an electrophile (H_2O, MeOH, IMe, or BrEt) (ratio electrophile:1 $\geq$ 3), the reaction mixture was hydrolyzed leading to a mixture of compounds, in which besides 2 and 3[13] (40–45% yield refered to 1) variable amounts (42–48% of the overall chemical yield) of other

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[13] Carbonyl compounds 2 and amines 3 are the same as those obtained by treatment of 1 with lithium under the same reaction conditions. See ref 1.

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