Tandem [4 + 2]/[3 + 2] Cycloadditions of Nitroalkenes. 13. The Synthesis of (−)-Detoxinine

Scott E. Denmark,* Alexander R. Hurd, and Hubert J. Sacha

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Received December 10, 1996[⊗]

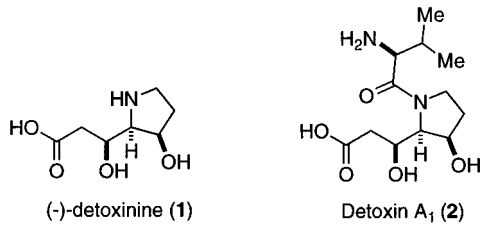
(−)-Detoxinine, an unusual, highly-functionalized amino acid, is the core residue of many components that comprise the detoxin complex. The synthesis of (−)-detoxinine was accomplished in 10 steps and 13.4% overall yield from commercially available dichlorodiisopropylsilane. The key step is an asymmetric tandem inter [4 + 2]/intra [3 + 2] cycloaddition between silyoxynitroalkene **17** and chiral vinyl ether (−)-**24**, illustrating the application of a temporary silicon tether in the tandem nitroalkene cycloaddition process.

Introduction

The detoxin complex is a collection of 12 unique depsipeptides (**2**−**13**), isolated from Streptomyces *caespitosus* var. *detoxicus* 7072 GC_1, which displays an intriguing detoxifying effect against the nucleoside antibiotic blasticidin S, Figure 1.[1,2] Coadministration of blasticidin S and the detoxin complex reduces the cytotoxicity of the antibiotic without reducing the curative effect in the treatment of rice blast disease.[3] Ten of the twelve characterized depsipeptides (**2**, **5**−**13**) of the detoxin complex possess the unusual amino acid (−)-detoxinine as the core scaffold. The absolute configuration of (−)-detoxinine (**1**) was assigned by chemical synthesis from D-glucose.[4]

Although (−)-detoxinine is not known to possess any particular biological activity of its own, the incorporation of unusual amino acids into peptide structures can promote interesting and unusual biological responses.[5] Besides the obvious interest in highly functionalized amino acids, the synthesis of detoxinine has also been undertaken to illustrate new synthetic methods and has previously been reported for both enantiomers and the racemate.[6] Most of the syntheses are fundamentally similar, utilizing an acetate aldol addition as a major bond-forming event either before pyrrolidine ring formation[6b] or with the pyrrolidine ring intact.[6a,c,e] Additionally, most syntheses originate with chiral pool starting material.

Recent reports from these laboratories have described the application of asymmetric tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition reactions[7−10] in the synthesis of natural products, Chart 1. These reports have highlighted a general method for the asymmetric synthesis of pyrrolizidine alkaloids, exemplified by the synthesis of (−)-hastanecine,[11] (−)-rosmarinecine,[12] and (+)-crotanecine.[13] Additionally, a synthesis of the *Sceletium* alkaloid (−)-mesembrine has been completed which



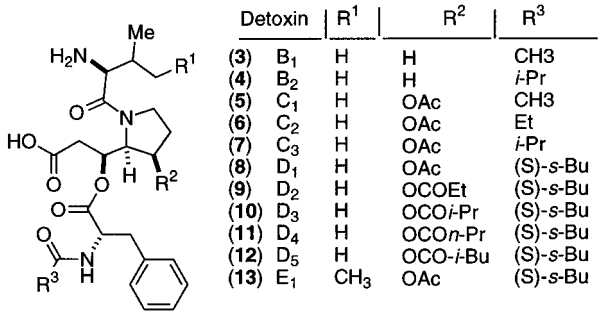


Figure 1. The detoxin complex.

[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1997.

(1) Yonehara, H.; Seto, H.; Aizawa, S.; Hidaka, T.; Shimazu, A.; Ótake, N. *J. Antibiot.* **1968**, *21*, 369.

(2) For a review of the detoxin complex, see Joullie, M. M.; Li, W.-R.; Han, S.-Y. *Heterocycles* **1993**, *36*, 359.

(3) Yonehara, H.; Seto, H.; Shimazu, A.; Aizawa, S.; Hidaka, T.; Kakinuma, K.; Otake, N. *Agr. Biol. Chem.* **1973**, *37*, 2771.

(4) Yonehara, H.; Otake, N.; Kakinuma, K. *Tetrahedron Lett.* **1980**, *21*, 167.

(5) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

(6) Racemic synthesis: (a) Häusler, J. *Liebigs Ann. Chem.* **1983**, 982. Natural (−) enantiomer syntheses: (b) Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133. (c) Joullie, M. M.; Ewing, W. R.; Harris, B. D.; Bhat, K. L. *Tetrahedron* **1986**, *42*, 2421. (d) Kogen, H.; Kadokawa, H.; Kurabayahi, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1240. Unnatural (+) enantiomer synthesis: (e) Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1996**, *61*, 566. Additionally, there are two formal synthesis of natural (−)-detoxinine on record. (f) Joullie, M. M.; Ewing, W. R. *Heterocycles* **1988**, *27*, 2843. (g) Takahata, H.; Banba, Y.; Tajima, M.; Momse, T. *J. Org. Chem.* **1991**, *56*, 240.

(7) (a) Denmark, S. E.; Dappen, M. S.; Cramer, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 1306. (b) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971. (c) Denmark, S. E.; Moon, Y.-C. ; Cramer, C. J.; Dappen, M. S.; Senanayake, C. B. W. *Tetrahedron* **1990**, *46*, 7373. (d) Denmark, S. E.; Kesler, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912.

(8) (a) Denmark, S. E.; Senanayake, C. B. W.; Ho, G.-D. *Tetrahedron* **1990**, *46*, 4857. (b) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1991**, *56*, 6738. (c) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859. (d) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205.

(9) (a) Denmark, S. E.; Moon, Y.-C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (c) Denmark, S. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1853. (d) Denmark, S. E.; Senanayake, C. B. W.; Schnute, M. E.; Moon, Y.-C.; Ho, G.-D.; Middleton, D. S. *Proceedings of the Fifth International Kyoto Conference on New Aspects of Organic Chemistry*; VCH Verlagageselschaft and Kodansha, Ltd. 1992. (f) Denmark, S. E.; Stolle, A.; Dixon, J. A.; Guagnano, V. *J. Am. Chem. Soc.* **1995**, 117, 2100.

(10) (a) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3857. (b) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576. (c) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221.

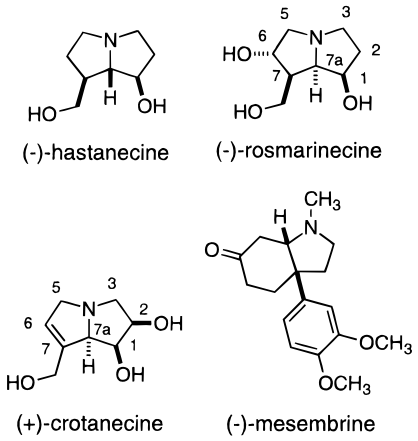
(11) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672.

(12) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266.

(13) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125.

S0022-3263(96)02306-7 CCC: $14.00

Chart 1



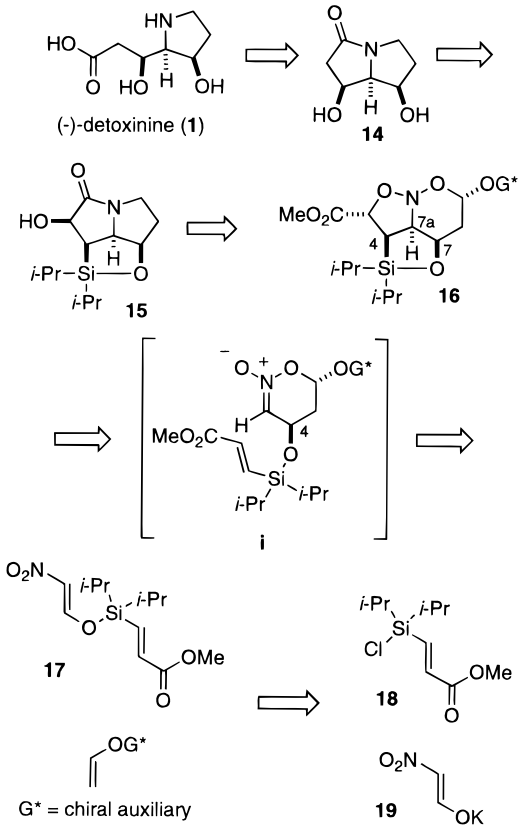
employed a tandem cycloaddition as the key step.[14] For the syntheses of the rosmarinecine and crotanecine the critical *cis*-relationship between HC(1) and HC(7a) was established by an intramolecular [3 + 2] cycloaddition through an ester linkage. This also provided the requisite functionality for the C(7) hydroxymethyl group common to these structures. (−)-Detoxinine, however, bears a simple hydroxyl group in this position and therefore requires a tether capable of linking the nitroalkene and the dipolarophile without carbon atoms. The synthesis of (−)-detoxinine thus represented a challenge to extend the scope of the tandem cycloaddition process in the realm of possibilities for the connecting tether. The successful resolution of this challenge in the synthesis of (−)-detoxinine is detailed below.

Synthesis Design

An alternative tether in the tandem nitroalkene cycloaddition process for the synthesis of (−)-detoxinine had to incorporate the following design features: (1) the removal of the tether must reveal hydroxyl or equivalent functional groups at both points of attachment, (2) the tether must be limited to two atoms to achieve proper diastereocontrol, and (3) most importantly, the nitroalkene must be competent in the tandem cycloaddition reaction itself. A temporary silicon tether presented an alternative device which could satisfy these criteria. The use of a silyloxy linkage between the nitroalkene and the dipolarophile could provide the appropriate diastereocontrol, yet allow for proper functionalization by the Tamao−Fleming oxidation.[15] A temporary silicon tether has been employed as a powerful strategy for diastereocontrol in many reactions including cycloadditions.[16,17]

In designing a synthetic approach to (−)-detoxinine, we recognized that the natural product would be accessible by hydrolysis of bicyclic lactam **14**, Scheme 1. The lactam **14** was envisioned to arise by α-deoxygenation

Scheme 1



followed by tether excision using the Tamao−Fleming oxidation[15] of hydroxy lactam **15**. Hydroxy lactam **15** would itself be derived from hydrogenolytic unmasking of nitroso acetal **16**, which is the basic subunit created in the tandem cycloaddition process.

Nitroalkene **17** was formulated for the synthesis of nitroso acetal **16** with consideration of the following stereocontrol features. First, the C(7) configuration of nitroso acetal **16** would be established as C(4) in the intermediate nitronate **i** by an asymmetric [4 + 2] cycloaddition using an enantiomerically pure chiral vinyl ether and an appropriate Lewis acid. This stereocenter then controls the relative (and conseqently absolute) configuration of the remaining stereocenters. Second, the C(7a) configuration in nitroso acetal **16** would be established as a result of the intramolecular [3 + 2] cycloaddition. Third, to establish the correct configuration at C(4) in nitroso acetal **16**, the [3 + 2] cycloaddition must occur with the tether folded in an endo fashion. Numerous studies have established the strong preference for an endo orientaion when a "two-atom" tether connects the nitroalkene and the dipolarophile.[9a] Nitroalkene **17** should be readily prepared from the coupling of chlorosilane **18** and potassium nitroacetaldehyde (**19**).[18] **19** has been featured in all three pyrrolizidine syntheses and this silicon-based dipolarophile finds its origins in analogy to the dienophiles employed by Stork[16a] and Sieburth.[16b] Thus, our first challenge was the selection of appropriate spectator groups on silicon and a protocol for the new tandem process.

Results

Orienting experiments aimed at assaying the stability of β-(silyloxy)nitroalkenes established that bulky sub-

(14) Denmark, S. E.; Marcin, L. R., *J. Org. Chem.* **1997**, *62*, 1675.

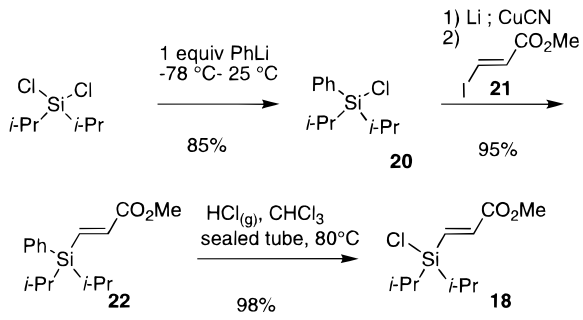
(15) (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (b) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37. (c) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. (d) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317.

(16) (a) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578. (b) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279. (c) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478. (d) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253.

(17) For a recent example of the use of the temporary silicon tether in [3 + 2]-dipolar cycloadditions of nitronates see: Righi, P.; Marotta, E.; Laduzzi, A.; Rossini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446.

(18) Babievskii, K. K.; Belikov, V. M.; Tikhohova, N. A. *Bull. Acad. Sci. USSR (Engl. Transl.)* **1970**, 1096.

Scheme 2



stituents (e.g. TIPS, TBS) were necessary. The isopropyl groups were selected to balance product stability with reactivity of the chlorosilane precursors and ease of synthesis. The preparation of chlorosilane **18** was initially envisioned by the addition of silyl anions to carbon−carbon multiple bonds.[19] The reaction of the lower order (phenyldiisopropylsilyl)cyanocuprate with methyl propiolate provided exclusively phenylsilane (*E*)-**22** albeit in unsatisfactory (40−68%) yields. As an alternative, the coupling of silylcopper reagents to haloalkenes was considered. Although the addition of silyl anions to α,β-unsaturated esters has been reported by several groups,[20] the addition of such cuprates to β-haloacrylates was unknown. Since both carbocuprates[21] and stannyl cuprates[22] couple with retention of configuration, the addition of silyl cuprates (specifically phenyldiisopropylsilyl) to β-iodoacrylates was investigated.

To accomplish this an improved synthesis of phenyldiisopropylsilyl chloride (**20**)[23] was first developed by the monoaddition of phenyllithium to dichlorodiisopropylsilane in 85% yield, Scheme 2. The silyllithium reagent, prepared by a modified Lambert procedure,[24] was treated with 1 equiv of CuCN at −20 °C for 30 min, and then the copper reagent was added to a −105 °C solution of iodoacrylate **21**[25] affording phenylsilane **22** in 95% yield.[26]

Our initial plan was to carryout the protodesilylation of **22** to create a triflate or fluoride. However, the dearylation of **22** proved to be more challenging than anticipated. For example, protodesilylation with triflic acid, tetrafluoroboric acid, or boron trifluoride acetic acid complex formed the silyl triflate or silyl fluoride but only in low yield and accompanied by inseparable hydrolysis products and starting material. Ultimately, an extremely clean protodesilylation could be affected with excess (30 equiv) dry HCl in chloroform at 80 °C (Carrius tube).

Scheme 3

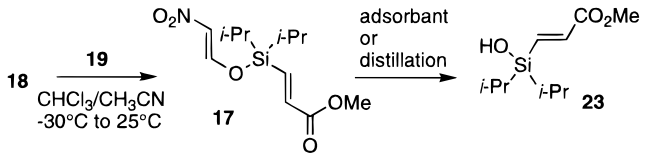
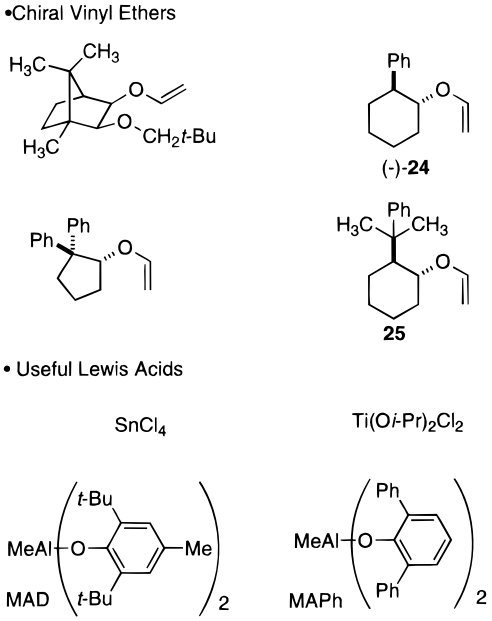


Chart 2



After being heated for 2 h, phenylsilane **22** was converted to chlorosilane **18** in 98% yield (distilled).

The coupling of chlorosilane **18** with potassium nitroacetaldehyde (**19**) provided nitroalkene **17** (Scheme 3), which was (despite the isopropyl groups), unfortunately, not amenable to purification. Attempted distillation (4.5×10^{-5} Torr), chromatography (silica plug, silica Et_3N complex plug, basic alumina III plug), and even cold chromatography (neutral alumina III, −30 °C) resulted in isolation of only the hydrolysis product **23** (see Supporting Information). Consequently, **17** had to be used directly in the next step.

The next and most critical reaction to investigate was the tandem process itself. The flexibility of the asymmetric tandem nitroalkene cycloaddition method derives from the many combinations of Lewis acids and chiral vinyl ethers[8] which are available for optimization studies, Chart 2. Methylaluminum bis-(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[27] and Ti(O*i*-Pr)$_2$Cl$_2$ both proved to be poorly selective promoters for cycloadditions between chiral vinyl ether **24**[8c] and nitroalkene **17**. Methylaluminum bis(2,6-diphenylphenoxide) (MAPh)[27] was found to be the Lewis acid of choice, as nitroso acetal **16** was produced with excellent selectivity (*ca* 30:1) using either chiral vinyl ether **24** or **25**.[8d] Ultimately, **24** was chosen because of the ease of preparation of *trans*-phenylcyclohexanol (**26**). The results of previous cycloadditions with 2-substituted nitroalkenes and this vinyl ether promoted by MAPh suggested that (−)-**24** should provide the correct enantiomer of detoxinine.[8c]

Unlike most nitroalkene cycloaddition procedures which display sensitivity to reagent stoichiometry, no discern-

(19) For a review of silyl anions see: Tamao, K.; Kawachi, A. In *Advances in Organometallic Chemistry*; Stone, F. G. A., West R., Eds.; Academic Press: New York, 1995; Vol. 38, Chapter 1, p 1.

(20) (a) Fleming, I.; Kindon, N. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1177. (b) Fleming, I.; Kindon, N. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 303. (c) Oppolzer, W.; Mills, R. J., Pachinger, W.; Stevenson, T. *Helv. Chim. Acta* **1986**, *69*, 1542. (d) Palomo, C.; Aizpurua, J. M.; Iturburu, M.; Urchegui, R. *J. Org. Chem.* **1994**, *59*, 240.

(21) Kozlowski, J. A. In *Comprehensive Organic Synthesis, Combining C-C π-Bonds*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991; Vol 4; p 169.

(22) (a) Seitz, D. E.; Lee, S.-H.; *Tetrahedron Lett.* **1981**, *22*, 4909. (b) Piers, E.; Morton, H. E.; Chong, J. M. *Can. J. Chem.* **1987**, *65*, 78. (c) Piers, E.; Morton, H. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1033.

(23) (a) Weidenbruch, M.; Schiffer, W.; Hägele, G.; Peters, W. *J. Organomet. Chem.* **1975**, *90*, 145. (b) Hurd, C. D.; Yarnall, W. A. *J. Am. Chem. Soc.* **1949**, *71*, 755. (c) Metras, F.; Plazanet, J.; Valade, J. *Bull. Soc. Chim. Fr.* **1966**, 2155.

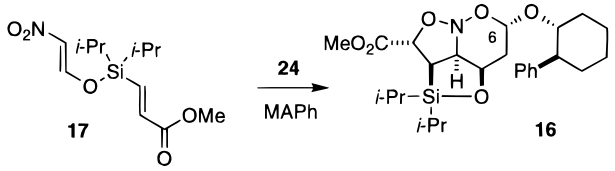
(24) Lambert, J. B.; Urdaneta-Pérez, M. *J. Am. Chem. Soc.* **1978**, *100*, 157.

(25) Biougne, J.; Théron, F. *C. R. Acad. Sc. Paris* **1971**, *272*, 858.

(26) Higher order silylcyanocuprates provided the β-silyl unsaturated ester in low yield. Additionally, multiple addition products were suspected as byproducts. Investigations with alternative copper source also failed.

(27) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. (b) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316. (c) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 9011. (d) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.

Table 1. Cycloadditions of 17 and 24



entry	*T*, °C	*t*, h	yield, %	dr[a]
1	−80	4	44	>25:1
2	−85	18	37	>25:1
3	−85	18	59	>25:1
4	−85	17	53	>25:1
5	−55	3.5	60	17:1
6	−30	3.5	65	13:1

[a] The diastereomer ratio was determined by 400 MHz ^{1}H NMR using a 90° pulse width and 5 s delay time.

ible advantage was noticed using 1−3 equiv of both vinyl ether and Lewis acid, and ultimately, 2 equiv of each were used. A slight yield and selectivity dependence on reaction temperature was noticed, Table 1. The diastereomeric ratio was highest at low temperatures, but the yield was variable and could not be increased with extended reaction times (entries 1−4).[28] As the reaction temperature was increased (entries 5 and 6), a drop in selectivity was compensated by a slight boost in yield.

The optimized procedure involved addition of MAPh to a −78 °C solution of **17** and (−)-**24**, followed by slow warming to −15 °C over 14.5 h, Scheme 4. Nitroso acetal (+)-**16** was isolated after workup and chromatography in a satisfactory 60% yield (two steps) as an inseparable 27/1 mixture of diastereomers. Additionally, 1.16 equiv of chiral alcohol (−)-**26** was recovered. The nitroso acetal (+)-**16** was assigned as arising form an exo mode [4 + 2] cycloaddition by ^{1}H NMR analysis of HC(6) and correlation with established precedent.[8,9b,13] It could not be determined whether the minor diastereomer results from an endo mode [4 + 2] cycloaddition or an exo mode [4 + 2] cycloaddition with the opposite facial selectivity. In no instances was the intermediate nitronate detected.

The hydrogenolysis of nitroso acetal (+)-**16** was dependent upon hydrogen pressure and time. Under optimal conditions (Raney nickel, 100 psi H_2, MeOH, 48 h) a 51% yield of hydroxy lactam (−)-**15** and a 93% recovery of chiral alcohol (−)-**26** was realized (Scheme 4).[29] Additionally, **27**, tentatively assigned as Peterson olefination product,[30] was isolated in 18% yield. Control experiments established that **27** was a primary product. Hydroxy lactam (−)-**15** could not be converted to **27** either by heating or exposure to the hydrogenolysis reaction conditions. Attempts to minimize the Peterson olefination pathway by solvent change and the use of additives (HOAc, H_2O, $CeCl_3$, and Ti(O*i*-Pr)$_4$) as well as buffered solutions (pH = 5.5 and 7.8) were to no avail.

Having installed all the stereocenters of (−)-detoxinine, the remaining transformations necessary were α-deoxygenation, silyl oxidation, and hydrolysis. Hydroxy lactam (−)-**15** was converted to thionocarbonate (−)-**28** in 85% yield, which also permitted a convenient determination of enantiomeric purity (>99% ee by chiral HPLC, Regis, *R*,*R*-Whelk-O1). Barton−McCombie radical deoxygenation[11,31,32] of thionocarbonate (−)-**28** afforded lactam (−)-**29** in 84% yield. Tamao−Fleming oxidation[15] of the silyloxy tether was accomplished using tetrabutylammonium fluoride and hydrogen peroxide at 60 °C, providing lactam diol (−)-**14** in 86% yield (Scheme 4). Lactam hydrolysis was affected with refluxing 10% aqueous hydrochloric acid for 13 h. Following purification by cation exchange chromatography and subsequent trituration with hot ethanol to remove olefinic by-products, (−)-detoxinine (**1**) was isolated in 90% yield.[33] The physical properties of synthetic material matched those reported. Mp = 227−229 °C dec, $[\alpha]^{20}_D = -4.4°$ (H_2O, *c* = 0.50); lit.[6b] mp = 225−228 °C, $[\alpha]_D = -4.8°$ (H_2O, *c* = 0.50).

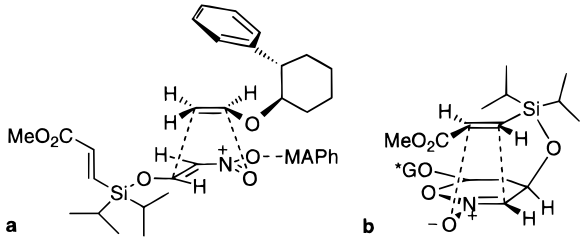


Figure 2. (a) [4 + 2] Cycloaddition: proposed approach of vinyl ether (−)-**24** to nitroalkene **17**. (b) [3 + 2] Cycloaddition: proposed endo (tether) approach of the dipolarophile to the same face of the nitronate dipole.

Unfortunately, a direct comparison of our synthetic material with a sample from natural sources was not possible. Additionally, the only reported physical or spectral property of natural detoxinine is a 100 MHz ^{1}H NMR of the hydrochloride salt in pyridine-d_5.[34] A 500 MHz ^{1}H NMR of synthetic (−)-detoxinine hydrochloride salt in pyridine-d_5 is comparable to that in the literature and is provided (see Supporting Information). Furthermore, ^{1}H NMR, ^{13}C NMR, MS, and IR spectra of our synthetic material are nearly identical to the spectra of Häusler's synthetic racemic detoxinine (see Supporting Information).

Discussion

Tandem Cycloaddition. There are three factors which influence the stereochemical outcome of the [4 + 2] cycloaddition: (1) the endo/exo approach of the dieneophile and (2) the reactive conformation of the vinyl ether, as either *s-trans* or *s-cis*, and (3) the design of the chiral auxiliary. The stereochemical course of the [4 + 2] cycloaddition of nitroalkene **17** and (−)-**24** can be understood as an exo, *s-trans* approach of the vinyl ether to the *si* face of the nitroalkene, which is analogous to the previously described MAPh-promoted cycloadditions using this vinyl ether, Figure 2a.[8b,c,9b,d]

The selectivity observed in the [3 + 2] cycloaddition is a direct consequence of the constraints imposed by the two-atom tether as previously noted.[9a] Nitroso acetal (+)-**16** results from a [3 + 2] cycloaddition to the same face of the nitronate dipole to which the tether is attached. Additionally, the tether is folded endo, and thus, the carbomethoxy substituent of the dipolarophile is oriented in an exo fashion, Figure 2b.

(28) A similar observation was documented for nitroalkene bearing a 2 methylene tether with MAPh and bornanediol derived chiral vinyl ether. M. E. Schnute, Ph. D. Thesis, University of Illinois, 1995.

(29) Recovered (−)-**26** from all hydrogenolysis reactions was determined to be of >99% ee by chiral HPLC (R,R-Whelk-O1, Regis).

(30) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Ager, D. J. *Synthesis* **1984**, 384. (c) Ager, D. J. *Org. React.* **1990**, *38*, 1.

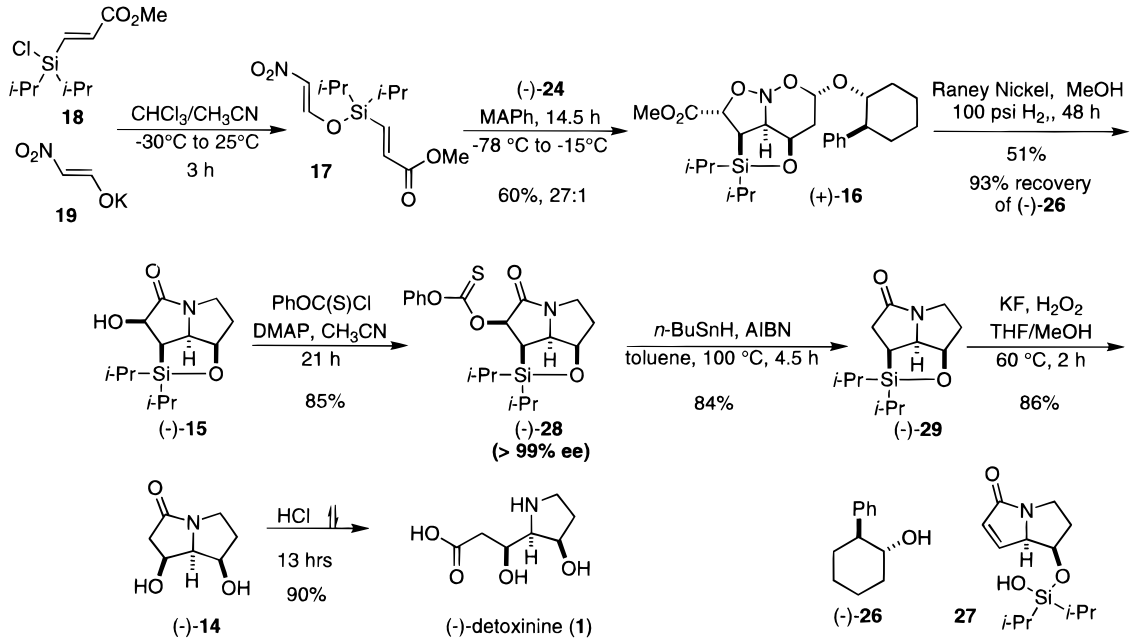
(31) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(32) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.

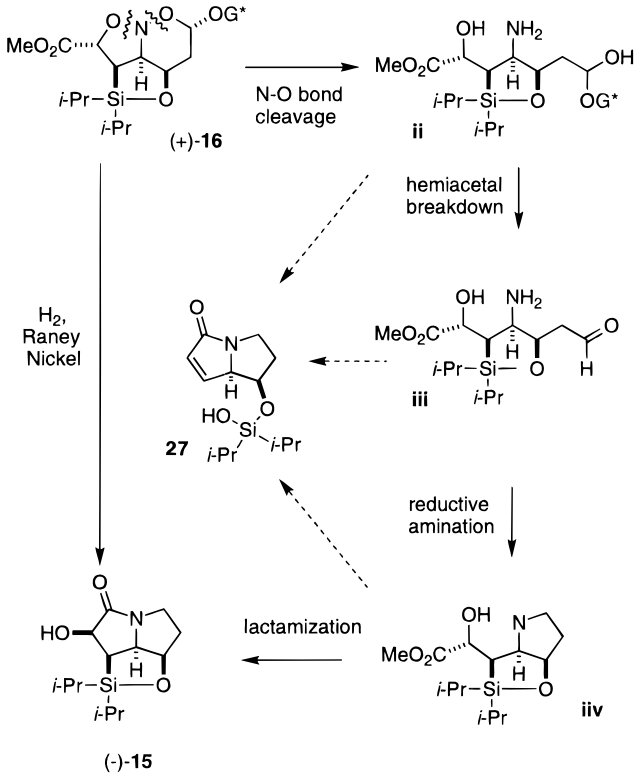
(33) Danishefsky, S.; Dynak, J. *J. Org. Chem.* **1974**, *39*, 1979.

(34) Yonehara, H.; Otake, N.; Kakinuma, K. *Agr. Biol. Chem.* **1974**, *38*, 2529.

Scheme 4



Scheme 5



Hydrogenolysis. The hydrogenolysis of nitroso acetals to hydroxy lactams is a remarkable transformation which deserves comment. It is believed that the process involves a series of discrete steps as shown Scheme 5. Double N−O bond cleavage produces hemiacetal **ii** which breaks down to amino aldehyde **iii.** Amino aldehyde **iii** undergoes imine formation and saturation to pyrrolidine **iv** followed by lactamization. Since the timing of individual steps is critical to the overall yield of hydroxy lactam, hydrogenolysis of each nitroso acetal warrants individual optimization.

The isolation of only one byproduct of this reaction provides little insight into the sources of material loss. This is especially true as it is not clear from which intermediate(s) the unsaturated lactam **27** originates, but at any point in the acyclic form, both the *syn* and *anti* elimination processes are available. The use of buffered solutions (pH = 5.5, 7.8) as cosolvents and even aqueous methanol solutions failed to alter the product ratio. It is also possible that lactamization was slow due to generation of ring strain in the tricyclic hydroxy lactam **27**[12,13] and, as a result, greater opportunity for the Peterson process to occur. However, attempts to accelerate this step with additives ($Ti(O\textit{i}\text{-}Pr)_4$ or $CeCl_3$) were unsuccessful.

The enantiomeric enrichments of the intermediates were accurately determined and deserve brief comment. After silica gel chromatography, thionocarbonate (−)-**28** was determined to be 92% ee by chiral HPLC. Since this material originated from nitroso acetal (+)-**16** of 89% de, some enrichment occurred, likely due to differential rates of hydrogenolysis of nitroso acetal diastereomers. The remaining enrichment to >99% ee occurred during a single recrystallization of thionocarbonate (−)-**28**.

The facile oxidation of silane (−)-**29** is noteworthy considering the documented resistance of hindered silanes to oxidation.[15a,35] The fact that silane (−)-**29** was readily oxidized suggests this process was facilitated by release of ring strain.

Synthetic Summary

The synthesis of (−)-detoxinine (**1**) was accomplished in 10 steps and in a respectable 13.4% overall yield from commercially available dichlorodiisopropylsilane, making this the most selective (27/1) and shortest synthesis of detoxinine to date. All stereocenters were properly installed in a single tandem cascade event. However, most noteworthy is the successful demonstration that the temporary silicon tether provides exceptional diastereoselectivity, and that the vestige of the tether can be completely removed, leaving as its legacy two newly created hydroxyl stereocenters. The synthesis of more

(35) (a) Andry, O.; Landais, Y.; Planchenault, D. *Tetrahedron Lett.* **1993**, *34*, 2927. (b) For a useful protocol for the oxidation of hindered silanes, see Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044.

complex natural products using asymmetric, tandem [4 + 2]/[3 + 2] nitroalkene cycloadditions is currently in progress.

Experimental Section

General Experimental. See Supporting Information for details.

Chlorodiisopropylphenylsilane (20). Phenyllithium (34.5 mL, 50.0 mmol, 1.45 M in cyclohexane/Et_2O, 1.0 equiv) was added slowly (45 min) via syringe pump to a cold (−73 °C) solution of dichlorodiisopropylsilane (9.0 mL, 49.9 mmol, 1.0 equiv) in 50 mL of Et_2O. After 30 min, precipitation of salts was observed. After the addition was complete, the mixture was allowed to warm to rt over 2.5 h and was stirred for an additional 2 h. Hexane (50 mL) was added, and the slurry was Schlenk filtered. The filtrate was concentrated and fractionally distilled through a 10 cm vacuum-jacketed, Vigreaux column to afford 9.59 g (85%) of **20** as a clear, colorless liquid. Data for **20**: bp 48−52 °C (0.03 Torr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6−7.63 (m, 2 H), 7.39−7.44 (m, 3H), 1.43 (sept, J = 7.3, 2H), 1.10 (d, J = 7.3, 6H), 1.02 (d, J = 7.4, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.18, 132.02, 129.84, 127.69, 16.86, 16.63, 13.6; IR (neat) 2948 (s), 1464 (s), 1428 (s); MS (70 ev) 226 (M^+, 13), 155 (100). Anal. Calcd for $C_{12}H_{19}ClSi$ (226.82): C, 63.54; H, 8.44; Cl, 15.63. Found: C, 63.45; H, 8.34; Cl, 15.86.

(Diisopropylphenylsilyl)lithium A modification of the Lambert procedure was followed.[24] To a suspension of lithium shot (1.8 g, 259 mmol, 4.7 equiv) (washed with 3 × 10 mL hexane, and 10 mL of THF) in 50 mL of THF was added a solution of chlorodiispropylphenylsilane **(20)** (12.5 g, 55.1 mmol, 1.0 equiv) in 25 mL of THF. The mixture was sonicated for 3.5 h and stirred at rt for an additional 13 h. Excess lithium was removed through a Schlenk filter. The dark green filtrate was titrated by the method of Gilman[36] and determined to be 0.566 M.

Methyl (*E*)-3-(Diisopropylphenylsilyl)propenoate (22). To a suspension of CuCN (2.46 g, 27.5 mmol, 1.1 equiv) in 100 mL of THF at −20 °C was added (diisopropylphenylsilyl)-lithium solution (48.5 mL, 27.5 mmol, 1.1 equiv). The resulting wine-red solution was stirred for 30 min and was then cooled to −80 °C. The cuprate solution was added to a solution of iodoacrylate **21**[25] (5.30 g, 25 mmol) in 150 mL of THF at −105 °C. The solution was allowed to warm to 5 °C over 4 h and was then quenched with 100 mL of NH_4Cl solution and 80 mL of H_2O. The resulting mixture was extracted with TBME (4 × 200 mL). The organic extracts were washed with brine (4 × 15 mL), dried ($MgSO_4$), and concentrated. The resulting oil was purified by silica gel chromatography (hexane/EtOAc, 80/1, 50/1, 25/1) and distillation to afford 6.53 g (95%) of **22** as a clear, colorless oil. Data for **22**: bp 150−152 °C (0.25 Torr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.49 (m, 6H), 6.43 (d, J = 19.3, 1H), 3.78 (s, 3H), 1.36 (sept, J = 7.3, 2H), 1.10 (d, J = 7.3, 6H), 1.00 (d, J = 7.3, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.87, 143.79, 137.03, 135.24, 132.44, 129.3, 127.73, 51.71, 17.63, 10.55; IR (neat) 1731 (s); MS (70 eV) 276 (M^+, 9), 233 (100); TLC R_f = 0.59 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{16}H_{24}O_2Si$ (276.45): C, 69.52; H, 8.75. Found: C, 69.87; H, 8.35.

Methyl (*E*)-3-(Diisopropylchlorosilyl)propenoate (18). Hydrogen chloride was condensed into a cold (EtOH/N_2) graduated cylinder attached to a Carrius tube. The condensed HCl (3.4 mL, 111 mmol, 31 equiv) was allowed to transfer upon the removal of the cooling bath through a glass side arm into the Carrius tube containing a frozen (N_2) solution of **22** (986 mg, 3.57 mmol) in 6.2 mL of $CHCl_3$. The Carrius tube was then sealed, allowed to thaw, and was then placed in an 80 °C oil bath for 2 h. The tube was then cooled in an ice bath, and the HCl was carefully released above a concentrated aqueous solution of KOH. The $CHCl_3$ solution remaining in the Carrius tube was concentrated to a pale yellow oil and distilled to afford 837 mg (98%) of **18** as a clear, colorless oil. Data for **18**: bp 100 °C (0.2 Torr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 18.6, 1H), 6.53 (d, J = 18.6, 1H), 3.79 (s, 3H), 1.23 (sept, J = 7.3, 2H), 1.08 (d, J = 7.3, 6H), 1.05 (d, J = 7.3, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.54, 140.27, 138.08, 51.83, 16.78, 16.66, 13.65; IR (neat) 1732 (s); MS (CI, CH_4) 237 (26), 235 (M^+ + 1, 66), 217 (100). Anal. Calcd for $C_{10}H_{19}O_2SiCl$ (234.80): C, 51.15; H, 8.16. Found: C, 51.40; H, 8.18.

Methyl (*E*)-3-[Diisopropyl[(*E*)-[(2-nitroethenyl)oxy]]silyl]propenoate (17). All glassware was flamed-dried under nitrogen three times. To a cold (−29 °C, bath temperature) suspension of potassium nitroacetaldehyde[18] (**19**) (503 mg, 3.96 mmol) in 60 mL of $CHCl_3$ (distilled, stored over 4 Å molecular sieves, and filtered through basic alumina III just prior to use) and 20 mL of CH_3CN in a three-necked, round-bottom flask equipped with a Schlenk filter leading to an inverted three-necked round-bottom flask for the cycloaddition was slowly (over 10 min) added a solution of **22** (933 mg, 3.96 mmol, 1.0 equiv) in 20 mL of $CHCl_3$. The creamy white suspension was allowed to slowly warm to 5 °C over 2.5 h. The suspension was stirred for an additional 30 min at rt before Schlenk filtration into the second flask. For characterization purposes, a 2.5 mL (2.5%) of the solution of **17** was removed and concentrated. The remainder was concentrated *in vacuo* and used without further purification. Data for **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 10.3, 1H), 7.09 (d, J = 19.0, 1H), 7.07 (d, J = 10.5, 1H), 6.46 (d, J = 19.3, 1H), 3.80 (s, 3H), 1.27 (m, 2H), 1.08 (d, J = 7.4, 6H), 1.07 (d, J = 7.4, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.03, 156.52, 138.79, 137.54, 128.80, 52.01, 16.45, 11.69.

(2*S*,2a*S*,4a*R*,6*S*,7b*S*)-3,3-Diispropyl-6-[(1*S*,2*R*)-(2-phenylcyclohexyl)oxy]-octahydro-7b-methyl-3-sila-1,4,7-trioxa-7a-azabicyclopent[*c,d*]indene-2-carboxylic Acid Methyl Ester ((+)-16). Trimethylaluminum (3.86 mL, 7.72 mmol, 2 equiv) was added rapidly to a solution of 2,6-diphenylphenol (3.80 g, 15.43 mmol, 4 equiv) in 76 mL of toluene at rt. The resulting, clear yellow solution was allowed to stir for 30 min.

To a cold (−78 °C) solution of **17** (assumed 1.11g, 3.86 mmol) in 96 mL of toluene was added (over 3 min) a solution of (−)-**24**[8c] (1.57 g, 7.76 mmol, 2 equiv) in 21 mL of toluene. The resulting solution was stirred for 20 min before the MAPh solution was added slowly (over 60 min). During the addition a deep wine-red complex developed and persisted. The reaction was stirred at −78 °C for 4 h, at −70 °C for an additional 8 h, and was then allowed to warm to −15 °C over the 2.5 h. The reaction was quenched with 20 mL of MeOH and allowed to warm to rt. The resulting mixture was diluted with CH_2Cl_2 (500 mL) and was washed with water (2 × 250 mL) and brine (2 × 250 mL). Aqueous washes were back extracted with CH_2Cl_2 (3 × 200 mL). Combined organic extracts were dried ($MgSO_4$), filtered through Celite (3 cm plug), and concentrated. The resulting, pale-yellow oil was purified by silica gel chromatography (pentane/TBME; 9/1, 4/1, 3/1, 2/1, 1/1). Homogeneous fractions were concentrated and heated to 50 °C *in vacuo* to afford 1.128 g (60%) of **16** as a clear glass. Mixed fractions containing 2,6-diphenylphenol, (−)-**26**, and (−)-**24** were concentrated, and the vinyl ether was hydrolyzed (1/1, MeOH/1 N HCl, 1 h). Purification by silica gel chromatography afforded 3.62 g (95%) of recovered 2,6-diphenylphenol and 787 mg (4.46 mmol, 1.16 equiv) of recovered (−)-**26**. Data for **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.40 (m, 5 H), 5.07 (d, J = 7.5, 1H), 4.30 (ddd, J = 6.8, 3.4, 2.2, 1H), 4.23 (dd, J = 10.7, 6.8, 1H), 4.08 (dd, J = 7.6, 6.6, 1H), 3.87 (s, 3H), 3.57 (td, J = 10.3, 4.3, 1H), 2.52 (ddd, J = 12.5, 10.4, 3.8, 1H), 2.24−2.32 (m, 1H), 2.22 (dd, J = 10.7, 7.5, 1H), 1.80−1.89 (m, 2H), 1.78 (ddd, J = 14.6, 6.6, 3.4, 1H), 1.70−1.77 (m, 1H), 1.58−1.62 (m, 1H), 1.53 (ddd, J = 14.6, 7.6, 2.2, 1H), 1.24−1.50 (m, 4H), 1.05−1.25 (m, 2 H), 1.04 (d, J = 7.5, 3H), 1.0 (d, J = 7.5, 3H), 0.97 (d, J = 6.8, 3H), 0.96 (d, J = 6.9, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.37, 144.08, 127.95, 127.69, 126.19, 99.32, 83.11, 81.31, 78.90, 72.59, 52.39, 51.22, 34.50, 32.77, 31.53, 30.00, 25.68, 25.14, 17.21, 17.17, 17.12, 17.00, 12.10, 10.67; IR (CH_2Cl_2) 1754 (s), 1602 (w); MS (130 ev) 490 (M^+, 8), 159 (100); $[\alpha]^{23}_D$ = +34.9° (CH_2Cl_2, c = 1.09); TLC, R_f = 0.63 (pentane/TBME, 2/1). Anal. Calcd for $C_{26}H_{39}NO_6Si$ (489.69): C, 63.77; H, 8.03; N, 2.86. Found: C, 63.78; H, 8.18: N, 2.89.

(1*S*,5a*R*,7a*R*,7b*S*)-7,7-Diisopropyl-1-hydroxy-6-oxa-7-sila-octahydro-2*H*-cyclopenta[*g,h*]pyrrolizin-2-one ((−)-

(36) Gilman, H.; Cartledge, F. K. *J. Organomet. Chem.* **1964**, *2*, 447.

15). To a solution of (+)-**16** (1.06 g, 2.17 mmol) (dr = 13:1) in 110 mL of MeOH in a glass-lined steel autoclave was added Raney Nickel W-2 (washed 5 × 200 mL of MeOH). The autoclave was sealed, pressurized to 100 psi with H_2, and stirred at room temperature for 45 h. The H_2 was carefully released from steel autoclave, and the reaction mixture was filtered through Celite (4 cm). The filter cake was washed with 1 L of MeOH, and the filtrate was concentrated. The resulting pale yellow oil was purified by silica gel chromatography (pentane/TBME; 2/1; CH_2Cl_2/MeOH; 50/1, 10/1) to afford 354 mg (93%) of recovered (−)-**26** and a mixture of (−)-**15** and **27**. The mixture of products was further purified by radial chromatography (CH_2Cl_2/MeOH; 50/1) to afford 299 mg (51%) (−)-**15** as a clear oil and 105 mg (18%) **27** as a clear oil. An analytical sample of (−)-**15** was prepared by precipitation from EtOAc/hexane. Data for (−)-**15**: mp 104−105 °C (EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (d, J = 8.8, 1H), 4.50 (t, J = 3.7, 1H), 4.11 (dd, J = 5.9, 3.4, 1H), 3.63 (dt, J = 11.2, 8.7, 1H), 3.34 (bs, 1H), 3.18 (t, J = 10.9, 1H), 2.54 (dd, J = 8.7, 6.0, 1H), 2.18−2.36 (m, 2H), 1.18 (sept, J = 7.4, 1H), 1.08 (m, 1H), 1.03 (d, J = 6.6, 3H), 1.01 (d, J = 7.4, 3H), 0.97 (d, J = 6.8, 3H), 0.96 (d, J = 6.9, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.3, 78.6, 74.9, 65.4, 40.5, 34.2, 32.6, 17.1, 17.0, 16.9, 16.8, 13.1, 12.9; IR (CH_2Cl_2) 3300−3500 (br), 1702 (s); MS (CI, CH_4) 270 (M^+ + H, 100); $[\alpha]^{23}_D$ = −6.66° (CH_2Cl_2, c = 0.93); TLC, R_f = 0.50 (CH_2Cl_2/MeOH; 20/1). Anal. Calcd for $C_{13}H_{23}NO_3Si$ (269.42): C, 57.96; H, 8.60; N, 5.20. Found: C, 57.93; H, 8.51: N, 5.18.

(1*S*,5a*R*,7a*R*,7b*S*)-7,7-Diisopropyl-6-oxa-1-[(phenoxythiocarbonyl)oxy]-7-sila-octahydro-2*H*-cyclopenta[*g*,*h*]pyrrolizin-2-one ((−)-28). To a solution of (−)-**15** (198 mg, 0.735 mmol) in 15 mL of CH_3CN was added a mixture of DMAP (184 mg, 1.51 mmol, 2.0 equiv in total) and phenyl thionochloroformate (156 μL, 1.13 mmol, 1.5 equiv in total) in three equal portions every 90 min. After 21 h the clear, bright yellow solution was concentrated, and the resulting oil was purified by silica gel chromatography (hexane/EtOAc; 3/1, 1/1) to afford (−)-**28** which was determined to be 93% ee by chiral HPLC. Crude (−)-**28** was recrystallized (EtOAc/hexane) to afford 253 mg (85%) of (−)-**28** as a highly crystalline, white solid which was determined to be 99.1% ee by chiral HPLC. Data for (−)-**28**: mp 146−147 °C (EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.45 (m, 2H), 7.27−7.32 (m, 1H), 7.07−7.11 (m, 2H), 6.33 (d, J = 8.8, 1H), 4.57 (t, J = 3.7, 1H), 4.19 (dd, J = 6.0,3.5, 1H), 3.74 (dt, J = 11.5, 8.8, 1H), 3.26 (td, J = 10.6, 2.2, 1H), 2.95 (dd, J = 8.8, 6.1, 1H), 2.23−2.41 (ABX$_3$, υ_a = 943.9 Hz, J_{ax} = 8.7, 2.2; υ_b = 915.9 Hz, J_{bx} = 10.6, 8.7, 3.5; J_{ab} = 14.6, 2H), 1.25 (sept, J = 7.5, 1H), 1.09−1.18 (m, 1H), 1.12 (d, J = 7.3, 3H), 1.08 (d, J = 7.3, 3H), 1.02 (d, J = 7.1, 3H), 1.01 (d, J = 7.1, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 194.4, 168.8, 153.3, 129.4, 126.6, 121.7, 84.4, 78.8, 65.5, 41.0, 34.2, 30.6, 17.3, 16.9, 16.8, 16.5, 12.8, 12.7; IR (KBr) 1703 (s); MS (70 ev) 405 (M^+, 13), 252 (100); $[\alpha]^{23}_D$ = −110.8° (CH_2Cl_2, c = 0.993); HPLC t_R (−)-**28** 9.82 min (99.55%); t_R (+)-**28** 13.8 min (0.45%) (99.1% ee) (*R*,*R*-Whelk-01, 24% EtOAc in hexane, 1.0 mL/min); TLC, R_f = 0.29 (EtOAc/Hexane; 1/1). Anal. Calcd for $C_{20}H_{27}NO_4SSi$ (405.59): C, 59.23; H, 6.71; N, 3.45; S, 7.91 Found: C, 59.16; H, 6.68; N, 3.39; S, 7.78.

(6*R*,6a*S*,7*S*)-7,7-Diisopropyl-6-oxa-7-sila-octahydro-2*H*-cyclopenta[*g*,*h*]pyrrolizin-2-one ((−)-29). A solution of AIBN (43 mg, 0.259 mmol, 0.42 equiv) and *n*-Bu_3SnH (0.250 mL, 0.929 mmol, 1.5 equiv) in 6 mL of toluene was added slowly (over 15 min) to a solution of (−)-**28** (250 mg, 0.616 mmol) in 30 mL of toluene at 100 °C via a Teflon syringe needle through the top of the reflux condenser. The reaction was heated at 100 °C for 4.5 h and then concentrated. The resulting oil was purified by silica gel chromatography (hexanes/EtOAc, 3/1, 0/1) and distilled to afford 147 mg (−)-**29** (84%) as a clear, colorless oil. Data for (−)-**29**: bp 155−160 °C (0.03 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (td, J = 3.4, 2.7, 1H), 4.36 (dd, J = 7.0, 3.7, 1H), 3.65 (dt, J = 11.4, 8.4, 1H), 3.08−3.14 (m, 1H), 3.03−3.10 (m, 1H), 2.49 (d, J = 8.2, 1H), 2.27−2.32 (m, 2H), 2.02 (dd, J = 9.4, 7.0, 1H), 0.98−1.17 (m, 14H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.53, 79.18, 70.42, 40.49, 36.94, 35.41, 20.55, 17.18, 17.11, 17.07, 16.86, 12.61, 11.50; IR (KBr) 1714 (s); MS (CI, CH_4) 254 (M^+ + 1, 100), $[\alpha]^{20}_D$ = −26.0° ($CHCl_3$, c = 0.16); TLC, R_f = 0.37 (EtOAc); HRMS for $C_{13}H_{24}NO_2Si$ calcd: 254.1576208 actual: 254.156897.

(6*R*,6a*S*,7*S*)-6,7-Dihydroxy-hexahydropyrrolizin-2-one (14). Potassium fluoride (53.0 mg, 0.912 mmol, 1.7 equiv) and hydrogen peroxide (0.910 mL, 8.02 mmol, 15 equiv) were added to a solution of (−)-**29** (135 mg, 0.533 mmol) in 7 mL of THF/MeOH (1/1). The reaction mixture was heated in a 60 °C oil bath for 2 h and then allowed to cool to rt. Silica gel (1.0 g) was added to the reaction mixture and then concentrated. The resulting pale yellow powder was purified by silica gel chromatography (CH_2Cl_2/MeOH; 6/1) and recrystallized twice (acetone/hexane) to afford 71.8 mg (86%) of (−)-**14** as a highly crystalline, white solid. Data for (−)-**14**: mp 108−109 °C (acetone/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (td, J = 6.8, 2.6, 1H), 4.53 (td, J = 3.7, 2.2, 1H), 3.92 (br s, 2H) 3.88 (dd, J = 6.3, 3.4, 1H), 3.84 (dt, J = 11.5, 8.3, 1H), 3.11 (dddd, J = 11.5, 8.9, 3.6, 1.4, 1H), 2.99 (dd, J = 17.6, 7.3, 1H), 2.45 (dd, J = 17.6, 2.8, 1H), 2.09−2.22 (ABX$_3$, υ_a = 1083.3 Hz, J_{ax} = 8.9, 8.3, 4.0; υ_b = 1062.4 Hz J_{bx} = 8.3, 4.0, 2.2; J_{ab} = 13.7); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.06, 71.03, 68.02, 67.60, 45.13, 40.18, 35.85; IR (KBr) 3395 (s, br), 3257 (s, br), 3123 (s,br), 1651 (s); MS (70 eV) 157 (m^+, 17), 71 (100); $[\alpha]^{23}_D$ = −38.8° ($CHCl_3$, c = 1.02); TLC, R_f = 0.44 (CH_2Cl_2/MeOH; 6/1); thermogravimetric analysis, 3.8% H_2O. Anal. Calcd for $C_{20}H_{27}NO_{4S}Si\cdot 0.33H_2O$ (157.17): C, 51.53; H, 7.21; N, 8.58. Found: C, 51.59; H, 6.94; N, 8.57.

(3*R*)-3-Hydroxy-3-[(2*R*,3*S*)-3-hydroxy-2-pyrrolidinyl]-propionic Acid. (Detoxinine) ((−)-1). A solution of (−)-**14** (55.2 mg, 0.351 mmol) in 10% aqueous HCl was heated to reflux for 13 h. The light brown solution was purified by cation exchange chromatography (Dowex 50 × 8-200), eluting with 1 N NH_4Cl. The crude product was triturated twice with EtOH to afford 55.2 mg (90%) of (−)-**1** as a light yellow solid. Data for (−)-**1**: mp 227−229 °C dec, lit.[6b] mp 225−228 °C dec lit.[6e] mp 224−227 °C; ^{1}H NMR (500 MHz, D_2O) δ 4.51 (t J = 3.3, 1H), 4.33 (ddd, J = 9.0, 8.0, 4.6, 1H), 3.41−3.56 (m, 3H) 2.64 (dd, J = 15.7, 4.5, 1H), 2.44 (dd, J = 15.7, 7.8, 1H), 2.25 (dtd, J = 14.0, 10.5, 3.3, 1H), 2.13 (ddd, J = 14.0, 7.5, 2.6, 1H); ^{13}C NMR (100 MHz, D_2O) δ 178.71, 69.43, 68.72, 65.90, 42.68, 41.92, 32.78; IR (KBr) 3232 (s), 3212 (s), 3201 (s), 1628 (s); MS (CI, CH_4) 176 (M^+ + 1, 49), 158 (100); $[\alpha]^{20}_D$ = −4.4° (H_2O, c = 0.50), lit.[6b] $[\alpha]^{20}_D$ = −4.8° (H_2O, c = 0.50); lit.[6c] $[\alpha]^{23}_D$ = −4.1° (H_2O, c = 0.50); lit.[6d] $[\alpha]^{25}_D$ = −4.7° (H_2O,); TLC, R_f = 0.27 (*i*-PrOH/NH_4OH; 7/3). Anal. Calcd for $C_7H_{13}NO_4$ (175.19): C, 47.99; H, 7.48; N, 8.00. Found: C, 47.77; H, 7.52; N, 7.89.

Acknowledgment. We are grateful to the National Institutes of Health (GM-30938) for financial support. A.R.H. thanks the University of Illinois for a Graduate Fellowship. H.S. thanks the Deutsche Forschungs Gemeinschoft for a postdoctoral fellowship. We gratefully acknowledge the gift of (±)-detoxinine from Prof. M. M. Joullie (University of Pennsylvania).

Supporting Information Available: A complete listing of ^{1}H NMR and ^{13}C NMR names with assignments, infrared absorbances, and mass spectral fragments for all compounds described, experimental and spectroscopic data for the compounds **23** and **27**, along with ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of synthetic (−)-detoxinine and (±)-detoxinine (Häusler) are provided (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO962306N