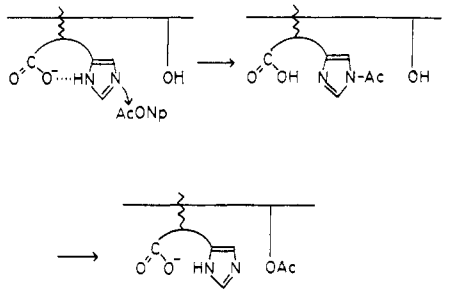
Scheme I



N-acetyl-**1b** than *N*-hexanoyl-**1b**.

These results suggest that the acyl transfer reaction is sensitive to the catalytic activity of the hydroxyl functions on the surfactants. This probably reflects the steric environment, acidity, and number (for **2c**) of surfactant hydroxyls. This behavior is associated with the incorporation of the acylimidazole intermediates on to the surface of the micelles, leading to an effective orientation for the attack of the hydroxyl groups. Thus, the reactions with **2c** give the largest deacylation rate enhancements: the relative deacylation rate constant ratio, based on **2a**, is 152 (PNPA, case 5) and 74 (PNPH, case 10).

Comparisons of the catalytic reactivities of **1b** and **1c** show that the acylation rates for the catalytic hydrolyses of PNPA and PNPH by **1b** in the presence of **2a** are greater than those by **1c** (cases 3 and 13, 8 and 14). This is consistent with intramolecular assistance provided by the carboxyl group to the imidazolyl group in **1b**.[14] However, the rate effect is small and the assistance is not definitively established by the data. It is also seen that the deacylation rate constants with **1b** are smaller than those with **1c**, in contrast to the opposite order of their acylation rate constants. The carboxylate anion of **1b** may stabilize the acylimidazolium group of the intermediate. In our previous papers, we also suggested that the carboxylate ion of **1b** enhanced the reactivity of the imidazolyl group in the catalytic enantioselective ester hydrolysis.[15] Recently, Murakami and co-workers showed that the carboxyl group of cationic peptide surfactants bearing both histidyl and aspartyl residues intramolecularly enhances the reactivity of the imidazolyl group.[16]

It is thus clear that the present functional micellar systems operate with nucleophilic acylation of the imidazolyl group, following which the hydroxyl group acts as an effective catalyst in the deacylation process. It is also suggested that the carboxylate group of **1b** interacts with the imidazolyl group so as to enhance the reactivity of the latter. All of the results are consistent with the mechanism given in Scheme I. Although, the esterolytic efficiency of these micellar catalytic systems is much lower than that of α-chymotrypsin, we find that the three functional groups are involved in the catalytic cycle of ester hydrolysis. This mode of action should be of considerable interest in connection with studies on the enzyme reaction since a key feature of the α-chymotrypsin-catalyzed hydrolysiss is basic activation by the Asp-Ser-His triad catalytic system.[17]

Acknowledgment. We are grateful to Professor Robert A. Moss for helpful comments.

Registry No. 1a, 2497-02-1; **1b**, 55258-10-1; **1c**, 78829-12-6; **2a**, 57-09-0; **2b**, 20317-32-2; **2c**, 42474-90-8; **2d**, 63989-29-7; **2e**, 84174-13-0; PNPA, 830-03-5; PNPH, 956-75-2; esterase, 9013-79-0; chymotrypsin, 9004-07-3.

(14) The acylation rate constants were measured at several concentrations of **2a** ($2.0–30 \times 10^{-3}$ M). The catalytic effects of both **1b** and **1c** were sensitive to **2a** concentration, but the ratios of the rates for **1b** compared to **1c** were essentially unchanged, suggesting that there was no significant structural difference between the mixed micelles of **1b** and **1c**. See also ref 15.

(15) Ihara, Y.; Hosako, R.; Nango, M.; Kuroki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 393; *J. Chem. Soc., Perkin Trans. 2*, in press.

(16) Murakami, Y.; Nakano, A.; Yoshimatsu, A.; Matsumoto, K. *J. Am. Chem. Soc.* **1981**, *103*, 2750.

(17) The hydrolysis of peptides catalyzed by α-chymotrypsin involves nucleophilic attack by the Ser-195 hydroxyl moiety.[3] However, for the hydrolysis of nonspecific substrates, Kirsch and Hubbard suggested that acylation of the enzyme would involve nucleophilic attack by the His-57 imidazole, followed by fast acyl transfer to the Ser-195 hydroxyl function: Kirsch, J. F.; Hubbard, C. D. *Biochemistry* **1972**, *11*, 2483.

Total Syntheses of *dl*-Gephyrotoxin and *dl*-Dihydrogephyrotoxin

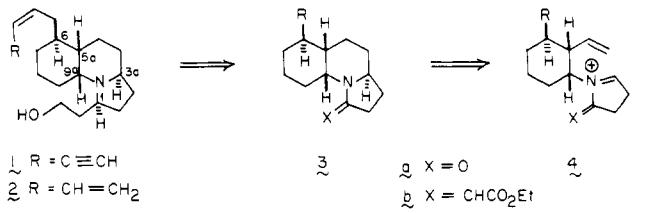
David J. Hart*† and Ken-ichi Kanai

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received July 6, 1982*

Abstract: A total synthesis of the Dendrobatid alkaloid *dl*-gephyrotoxin (**1**) has been achieved in 23 steps, using cyclohexenone, 1,3-butadiene, succinimide, ethyl bromoacetate, and propyne as carbon sources. A total synthesis of *dl*-dihydrogephyrotoxin (**2**), a structure tentatively assigned to a minor Dendrobatid alkaloid, is also described.

A number of alkaloids that possess interesting pharmacological properties have been isolated in minute quantities from skin extracts of frogs belonging to the Dendrobatid family.[1,2] These alkaloids have stimulated numerous synthetic studies,[3-10] and work on the synthesis of these natural products continues in laboratories throughout the world. Our interest in the Dendrobatid alkaloids has focused on gephyrotoxin (**1**), a muscarinic antagonist whose structure was determined by X-ray crystallographic analysis of its *p*-bromobenzoate.[11] This paper describes the details of studies

Scheme I



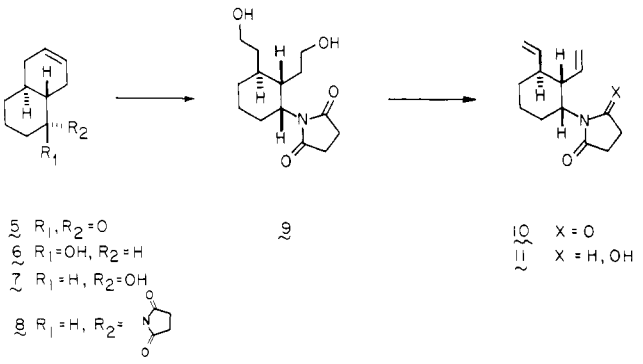
1 R = C≡CH
2 R = CH=CH$_2$
3
4 a X = O; b X = CHCO$_2$Et

that have culminated in a total synthesis of **1** and the related compound dihydrogephyrotoxin (**2**).[11]

† This paper is dedicated to my father and mother, Prof. Harold Hart and Geraldine Hart, on the occasions of their 60th birthdays and 40th wedding anniversary.

0002-7863/83/1505-1255$01.50/0

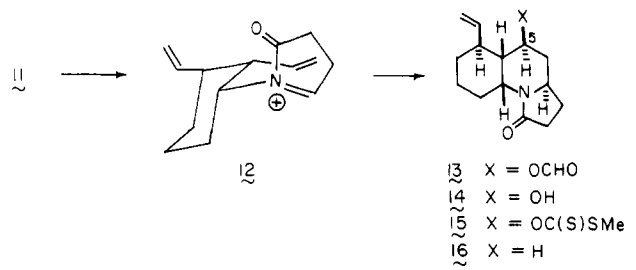
Scheme II



5 R_1,R_2 = O
6 R_1 = OH, R_2 = H
7 R_1 = H, R_2 = OH
8 R_1 = H, R_2 =
9
10 X = O
11 X = H, OH

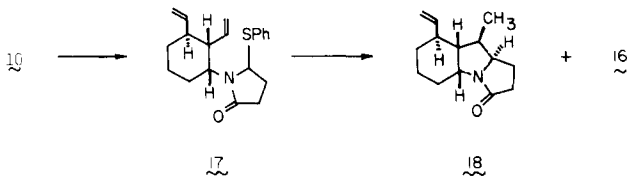
Our approach to gephyrotoxin is outlined antithetically in Scheme I. In planning a synthesis of gephyrotoxin we felt that the major stereochemical task would be establishing the configurations at C(1) and C(3a) relative to the three contiguous asymmetric centers at C(5a), C(6), and C(9a). We approached this problem by focusing on the *trans*-2,6-dialkylpiperidine moiety, a structural subunit of gephyrotoxin and a large number of other alkaloids.[12-14] While we were considering stereocontrolled routes to this structural subunit, the conformational behavior of *N*-acylpiperidines attracted our attention. It was known that 2-substituted *N*-acylpiperidines prefer to adopt conformations in which the C(2) substituent is axially disposed due to the presence of $A^{(1,3)}$ strain[15] in the alternative chair conformation.[16] This suggested that a tricyclic lactam of type **3** would be thermodynamically more stable than its C(3a) stereoisomer. Thus it appeared advantageous to pass through intermediates that were sp^2 hybridized at the incipient C(1) carbon of gephyrotoxin. Specifically, we hoped that the predicted greater thermodynamic stability of **3** relative to its C(3a) isomer would influence the stereochemical course of reactions used to establish the C(3a)

Scheme III



11
12
13 X = OCHO
14 X = OH
15 X = OC(S)SMe
16 X = H

Scheme IV



10
17
18
16

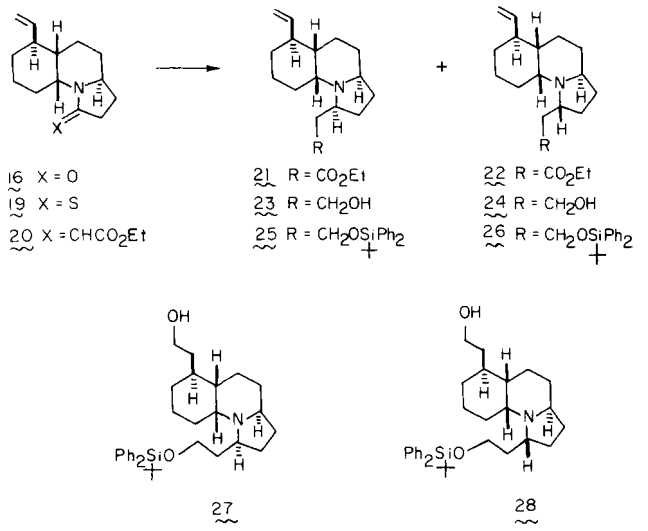
stereochemistry relative to preformed asymmetric centers at C(5a) and C(9a). Although several variants of this strategy were considered, we eventually decided to try to establish the C(3a) asymmetric center via cyclization of *N*-acyliminium or vinylogous *N*-acyliminium ions of type **4**.[17]

Model studies directed toward the synthesis of gephyrotoxin[18] and other alkaloids[19] confirmed that *N*-acyliminium ion cyclizations would provide a general route to bicyclic and tricyclic lactams containing *trans*-2,6-dialkyl-*N*-acylpiperidines as structural subunits. Therefore we set out to construct an appropriate precursor to an iminium ion of type **4** bearing a C(6) vinyl group (Scheme II). Treatment of cyclohexenone with 1,3-butadiene in the presence of aluminum chloride as described by Wenkert[20] gave the crystalline Diels–Alder adduct **5** in a 70% yield. When enone **5** was reduced with lithium aluminum hydride at room temperature, a 92% yield of a 4:1 mixture of equatorial alcohol **6** and its axial isomer **7**, respectively, was obtained. When the reduction was performed at −70 °C, however, the stereoselectivity improved and **6** was isolated in an 83% yield along with 9% of **7**. Treatment of **6** with succinimide under the conditions of Mitsunobu[21] gave the axial imide **8** as a viscous oil in a 62% yield. Thus, the first three steps of the synthesis established the relative stereochemistry at the incipient three contiguous asymmetric centers of gephyrotoxin.

The next task was to degrade **8** to *trans*-divinylcyclohexane **10**. Ozonolysis of **8** in methanol followed by a carefully monitored reduction with sodium borohydride gave crystalline diol **9** in yields ranging from 61 to 80%. When we first considered the task of converting diol **9** to diene **10** we were concerned about two potential problems. First, we thought that bisdehydration of **9** might be complicated by intramolecular oxepane formation.[22] In addition, we felt that it would be advisable to generate **10** under mild conditions because of potential stereochemical scrambling due to Cope rearrangements of the product.[23] The ^1H NMR spectrum of **9**, however, dispelled some of our worries. The C(9a) hydrogen in diol **9** appears at δ 4.22 as a doublet of triplets with coupling constants of 12, 4, and 4 Hz. This suggested that **9** adopts a chair conformation in which the β-hydroxyethyl groups both occupy axial sites. As a consequence of this conformational preference the C(5a) and C(6) side chains are not suitably disposed for oxepane formation, thus giving bimolecular processes a chance to compete. In the final analysis, treatment of **9** with tri-*n*-bu-

(1) For a thorough review see: Daly, J. W. *Fortschr, Chem. Org. Naturst.* **1982**, *41*, 206.
(2) Dendrobatid alkaloids have been divided into the batrachotoxin, histrionicotoxin, pumilliotoxin C, pumilliotoxin A, and gephyrotoxin classes of alkaloids.
(3) For approaches to batrachotoxins see: Imhof, von R.; Gössinger, E.; Graf, W.; Berner-Fenz, L.; Berner, H.; Schaufelberger, R.; Wehrli, H. *Helv. Chim. Acta* **1973**, *56*, 139.
(4) For approaches to histrionicotoxins see: Ibuka, T.; Mitsui, Y.; Hayashi, K.; Minakata, H.; Inubushi, Y. *Tetrahedron Lett.* **1981**, 4425 and references cited therein.
(5) For approaches to pumilliotoxin-C see: Hattori, K.; Matsumura, Y.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 7368 and references cited therein.
(6) For an approach to the pumilliotoxin A class see: Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851.
(7) For the first total synthesis of gephyrotoxin see: Fujimoto, R.; Kishi, Y.; Blount, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7154. For related studies examining the absolute configuration of **1** see: Fugimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981**, 4197.
(8) For syntheses of perhydrogephyrotoxin see: Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454. Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833. Also see ref 7.
(9) For another approach to gephyrotoxin see: Habermehl, G. G.; Thurau, O. *Naturwissenschaften* **1980**, *67*, 193.
(10) For a preliminary account of a portion of this work see: Hart, D. J. *J. Org. Chem.* **1981**, *46*, 3576.
(11) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128. An alkaloid that is a congener of gephyrotoxin is tentatively assigned structure **2** in this work.
(12) For applications of the approach described herein to other problems in alkaloid synthesis see ref 13 and 14.
(13) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555.
(14) Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1982**, *47*, 4403.
(15) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(16) For studies of the influence of allylic strain on conformations of *N*-acylpiperidines see: Chow, Y. L.; Colón, C. J.; Tam, J. N. S. *Can. J. Chem.* **1968**, *46*, 2821. Fraser, R. R.; Grindley, T. B. *Tetrahedron Lett.* **1974**, 4169. Quick, J.; Mondello, C.; Humora, M.; Brennan, T. *J. Org. Chem.* **1978**, *43*, 2705, and articles cited in ref 15. For another relevant study see: Mistryukov, É. A. *Bull. Akad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1963**, 838.
(17) For a recent review of *N*-acyliminium ion cyclization chemistry by the major contributor to the area see: Speckamp, N. *Rec Trav. Chim. Pays-Bas* **1981**, *100*, 345.
(18) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367.
(19) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.
(20) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Synth. Commun.* **1979**, *9*, 391.
(21) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(22) Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717.
(23) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 880.

Scheme V

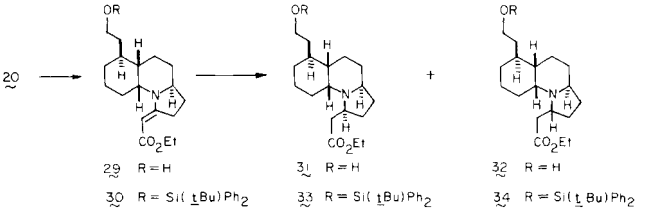


tylphosphine and *o*-nitrophenyl selenocyanate[22,24] followed by oxidation of the resulting bis(selenide) with hydrogen peroxide[25] gave diene **10** in a 76% yield. Analysis of the ^{1}H NMR spectrum of **10** revealed that it also adopted a chair conformation in which both vinyl groups were axially disposed. Therefore conformational constraints should also retard the rate at which **10** undergoes Cope rearrangements relative to similar *trans*-divinylcyclohexanes.

Treatment of **10** with diisobutylaluminum hydride[26] gave carbinolamide **11** in an 80% yield, completing the preparation of the required *N*-acyliminium ion precursor. Previously reported studies of the cyclizations of ions **3a** (R = H) and **3b** (R = H) suggested that both allylic strain effects and cyclohexane conformational preferences play a role in determining the stereochemical course of these reactions.[18,19] On the basis of the conformational prefernece of **10** described above, it was expected that these two effects would once again reinforce one another in the cyclization of *N*-acyliminium ion **12**. In fact, treatment of carbinolamide **11** with formic acid in dichloromethane gave tricyclic lactam **13** (79%) and alcohol **14** (1%). The undesired C(5) functionality was removed by saponification to alcohol **14** (99%), formation of xanthate **15** (92%), and reduction to lactam **16** (68–78%) with tri-*n*-butyltin hydride.[27] Several other methods of cyclizing **11** were investigated with the hope of obtaining a more direct route to lactam **16**. Although none of these attempts were as successful as the route described above (Scheme III), one reaction sequence is particularly noteworthy (Scheme IV). Treatment of **10** with sodium borohydride followed by thiophenol and a catalytic amount of *p*-toluenesulfonic acid gave a separable mixture of diastereomeric sulfides **17**. Treatment of **17** with tri-*n*-butyltin hydride and AIBN gave a 31% yield of the desired lactam **16** along with the isomeric lactam **18** (50%). Although this α-acylamino radical cyclization[28] followed a regiochemical course that was largely unproductive from the standpoint of preparing gephyrotoxin, that component which gave the desired regioisomer proceeded in the stereochemical sense that would be predicted based on the allylic strain and conformational arguments outlined above for the iminium ion cyclization.

With an appropriately substituted tricyclic ring system in hand, the C(1) side chain was introduced as outlined in Scheme V. Treatment of **16** with Lawesson's reagent[29] gave crystalline thiolactam **19** (95%), which was alkylated with ethyl bromoacetate. Treatment of the resulting alkylmercaptoalkylideniminium salt with triethylamine and triphenylphosphine gave vinylogous urethane **20** in an 84% yield.[30] We had hoped that a stereoelectronic effect, due to the known stability of *trans*-indolizidines relative to other indolizidine conformations,[31] would lead to production of the required C(1) stereochemistry upon hydride reduction of an iminium ion derived from vinylogous urethane **20**.[32] Unfortunately, little stereoselectivity was observed when **20** was reduced with sodium cyanoborohydride at pH 4 as isomeric amino esters **21** and **22** were isolated in 60% and 29% yields, respectively.[33] Nonetheless, to establish the stereochemical identities of **21** and **22**, a formal total synthesis of gephyrotoxin was completed as follows. Independent reduction of **21** and **22** with lithium aluminum hydride afforded alcohols **23** (91%) and **24** (97%), respectively. These alcohols were converted to the corresponding *tert*-butyldiphenylsilyl ethers **25** (100%) and **26** (93%).[34] Treatment of **25** and **26** with disiamylborane[35] followed by oxidation with hydrogen peroxide gave amino alcohols **27** (63%) and **28** (50%), respectively. The structure of **27** was confirmed by comparison with a sample of **27** generously provided by Professor Kishi. Since **27** had previously been converted to gephyrotoxin in Kishi's laboratories,[7] this constituted a formal total synthesis of *dl*-gephyrotoxin.

Scheme VI

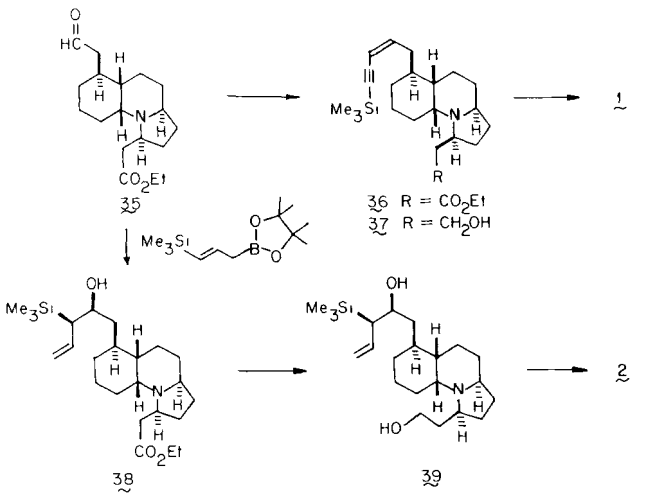


Substrate	Conditions	Yield	31 (33) : 32 (34)
29	50 psi H_2, Pt/Al_2O_3	84	32 : 68
30	50 psi H_2, Pt/Al_2O_3	96	96 : 4
29	$NaBH_3CN$, pH 4, MeOH	90	67 : 33
30	$NaBH_3CN$, pH 4, MeOH	92	65 : 35

Since the stereoselectivity in the cyanoborohydride reduction of **20** was disappointing, we sought alternative methods of converting this vinylogous urethane to gephyrotoxin. Inspired by the success of Kishi and Fujimoto in using remote functionality to control stereochemistry during the course of their elegant synthesis of gephyrotoxin,[7] we decided to introduce functionality into the C(6) side chain prior to reduction of the vinylogous urethane. Thus **20** was treated with disiamylborane[35] followed by oxidation with hydrogen peroxide to afford alcohol **29** (77%), which was converted to crystalline *tert*-butyldiphenylsilyl ether **30** (95%).[34] Prior to examining the stereochemical course of reductions of **29** and **30**, we prepared authentic samples of the expected reduction products **31–34** via sequential hydroxylation and etherification of olefinic esters **21** and **22**. With authentic samples of **31–34** in hand, alcohol **29** and ether **30** were reduced under a variety of conditions, two of which are shown in Scheme VI. These results show that the nature of the C(6) side chain has little effect on the course of iminium ion reductions ($NaBH_3CN$, pH 4) but profoundly influences the stereochemistry of catalytic hydrogenations. From the standpoint of the synthesis of gephyrotoxin, the best results

(24) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(25) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.
(26) Winterfeldt, E. *Synthesis* **1975**, 617.
(27) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(28) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430.
(29) Pederson, B. S.; Scheibye, S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.
(30) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.
(31) Skvortsov, I. M. *Russ. Chem. Rev.* (*Engl. Transl.*) **1979**, *48*, 262 and references cited therein.
(32) For elegant and encouraging studies see: Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 102, 103, and a reference cited therein. For less encouraging reports see: Sonnet, P. E.; Oliver, J. E. *J. Heterocycl. Chem.* **1975**, *12*, 289.
(33) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(34) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(35) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 1241.

Scheme VII



were obtained when **29** was hydrogenated over platinum on alumina, using a 1:1 mixture of ethyl acetate and hexane as the solvent. Under these conditions the desired amino ester **33** was isolated in a 92% yield along with 4% of its C(1) isomer **34**. Thus it appears that C(6) side chain conformations in which the bulky *tert*-butyldiphenylsilyl group interferes with approach of the catalyst to the β face of the olefin play an important role in determining the stereochemical course of the hydrogenation.[36]

The synthesis of gephyrotoxin was completed by using the method of Yamamoto[37] to introduce the *cis*-enyne moiety (Scheme VII). Treatment of **33** with tetra-*n*-butylammonium fluoride in tetrahydrofuran removed the *tert*-butyldiphenylsilyl directing group to afford hydroxy ester **31** in a 92% yield.[34] Swern oxidation[38] [$(COCl)_2$, Me_2SO, Et_3N] of **31** gave the unstable aldehyde **35** in a 78% yield. Treatment of **35** with the reagent derived from deprotonation of 1-(trimethylsilyl)-3-(*tert*-butyldimethylsilyl)-1-propyne with *tert*-butyllithium[37] gave a 30% yield of a 9:1 mixture of enyne **36** and the corresponding trans geometrical isomer.[39] Finally, reduction of **36** with diisobutylaluminum hydride followed by cleavage of the trimethylsilyl group from the resulting alcohol **37** (*n*-Bu_4NF, DMF) gave *dl*-gephyrotoxin (**1**) in a 94% yield.[40]

Aldehyde **35** also served as an intermediate in the synthesis of *dl*-dihydrogephyrotoxin (**2**). This transformation was accomplished by using a versatile diene synthesis recently developed by Matteson and Tsai.[41] Thus treatment of **35** with pinacol (*E*)-1-(trimethylsilyl)-1-propene-3-boronate[41] in dichloromethane at room temperature followed by hydrolysis of the resulting borate gave a quantitative yield of β-hydroxysilane **38** as a mixture of C(6) side-chain diastereomers.[42] Reduction of **38** with diisobutylaluminum hydride[43] afforded an 83% yield of diol **39**, which was converted to *dl*-dihydrogephyrotoxin (**2**) in a 60% yield upon treatment with an excess of potassium hydride in tetrahydrofuran.[44]

(36) For other uses of bulky groups to control the stereochemical course of reactions at remote centers see ref 7 and: Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616.

(37) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568.

(38) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(39) The isomer ratio was determined by integration of olefin and trimethylsilyl signals in the NMR spectrum of the mixture. The use of 1,3-bis(trimethylsilyl)propyne gave a 4:1 mixture of **36** and its geometrical isomer, respectively.

(40) Our *dl*-**1** was contaminated by approximately 5% of the trans geometrical isomer which gave an olefinic signal at δ 6.1 in the ^{1}H NMR spectrum of the mixture. Our material was identical with a sample of synthetic *d*-**1** kindly provided by Prof. Yoshito Kishi (TLC, IR, mass spectrum, 200-MHz ^{1}H-NMR) with the exception of a few upfield signals (δ 1.0–1.8 region) due to contaminants which appear in the ^{1}H NMR spectrum of our material.

(41) Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* **1981**, 2751.

(42) The ratio of diastereomers was shown to be roughly 1:1 by integration of the trimethylsilyl signals in the ^{1}H NMR spectrum of the product mixture.

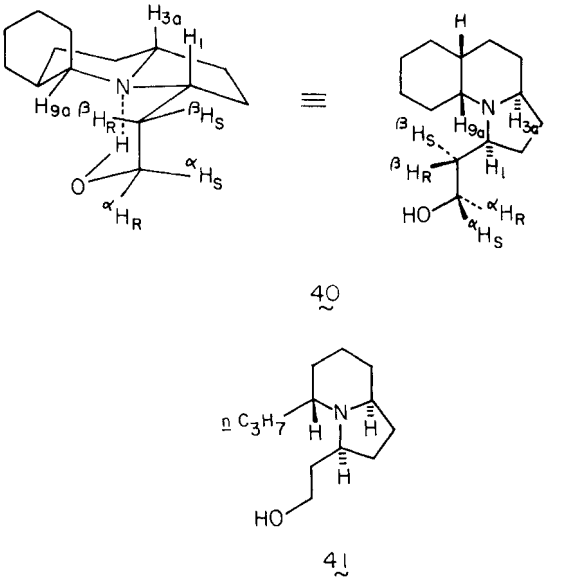
(43) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464.

Table I. Chemical Shifts and Multiplicities of Selected Carbinolamines

carbinolamine	chemical shift[a]					
	H_1[b,d]	H_{3a}[c,d]	H_{9a}[c,e]	$^{\alpha}H_S$[b,f]	$^{\alpha}H_R$[b,g]	$^{\beta}H_R$[b,h]
1	2.97	2.18	3.39	3.97	3.67	1.98
2	3.00	2.26	3.34	4.00	3.68	1.97
40	2.98	2.23	3.14	4.03	3.72	1.97
41	2.97	2.22	3.16	4.04	3.73	1.97

[a] Recorded in ppm downfield from internal Me_4Si in C_6D_6 at 200 MHz. [b] Assignment based on appropriate decoupling experiments. [c] Assignments based on multiplicities. [d] Signals were similarly shaped multiplets for each compound. [e] H_{9a} appeared as a doublet of triplets ($J \sim 12$, 4.5, and 4.5 Hz) in **1**, **2**, and **40** and as a multiplet in **41**. [f] $^{\alpha}H_S$ appeared as a triplet of doublets ($J \sim 11.5$, 11.5, and 3 Hz) for all four compounds. [g] $^{\alpha}H_R$ appeared as a doublet of triplets ($J \sim 11.5$, 4, and 4 Hz) for all four compounds. [h] $^{\beta}H_R$ appeared as an overlapping doublet of a doublet of triplets ($J \sim 14$–15, 10–12, and 4 Hz) for all four compounds.

During the course of these and related studies we also prepared carbinolamines **40** and **41**, substructures of gephyrotoxin and



dihydrogephyrotoxin. We examined the ^{1}H NMR spectra of **1**, **2**, **40**,[18] and **41** in an attempt to determine their solution conformational preferences. Some of the pertinent signals for these amino alcohols are listed in Table I. From the chemical shift data, we conclude that substituents on the indolizidine moiety of this series of compounds are identically disposed. The multiplicities of the three discernible C(1) side-chain protons in all four compounds suggest that the amino alcohol subunit adopts a conformation in which the hydroxyl and amino groups are intramolecularly hydrogen bonded. Furthermore, the coupling constants for H_{9a} in **1**, **2**, and **40** suggest that the C(9a) alkyl substituent is axially disposed in all of these compounds. All of these data are consistent with each molecule adopting a *trans*-indolizidine conformation similar to that shown for **40**.

In summary, stereoselective 23-step syntheses of *dl*-gephyrotoxin (**1**) and the related compound *dl*-dihydrogephyrotoxin (**2**) have been accomplished. An interesting feature of these syntheses is that no protection–deprotection reaction sequences were required. We have demonstrated that this route is adaptable to the synthesis of structural analogues of gephyrotoxin, several of which are undergoing biological evaluation.[45]

(44) The mass spectrum of **2** exhibited a fragmentation pattern similar to that reported for the natural product.[11] Unfortunately, samples of the natural alkaloid were not available for direct comparison with our material.

(45) We thank Dr. John W. Daly for his interest in evaluating our gephyrotoxin analogues.

Experimental Section

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H magnetic resonance spectra were recorded on Varian Associates EM-390, Bruker WP-200, or Bruker WM-300 spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants (in hertz), interpretation]. Infrared spectra were taken with a Perkin-Elmer 457 instrument. Mass spectra were recorded on an AEI-MS9 spectrometer. Samples on which exact masses were measured exhibited no significant peaks at m/e values greater than that of the parent. Combustion analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Solvents and reagents were dried and purified prior to use when deemed necessary: tetrhydrofuran and ether (distilled from sodium metal); methanol (distillation from magnesium methoxide); dichloromethane (passed through activity I alumina); toluene and *N,N*-dimethylformamide (distilled from calcium hydride). Reactions requiring an inert atmosphere were run under a blanket of nitrogen or argon. Analytical thin-layer chromatography was performed by using EM Laboratories glass-backed 0.25-mm precoated silica gel 60 F-254 plates and EM Laboratories glass-backed 0.25-mm precoated alumina oxide 60 F-254 plates. Column chromatography was performed over EM laboratories silica gel 60 (70–230 mesh) and Woelm neutral alumina.

***rel*-(4a*S*,8a*S*)-1,2,3,4,4a,5,8,8a-Octahydronaphthalen-2-one (5).** To a slurry of 19.3 g (0.145 mol) of aluminum chloride in 200 mL of benzene was added 15.5 g (0.16 mol) of cyclohexenone in one portion at room temperature. The resulting warm solution was stirred for 45 min followed by the addition of 25 g (0.46 mol) of 1,3-butadiene. The mixture was warmed at 70–75 °C (internal) for 5 h with the aid of a dry ice–acetone condenser. The resulting mixture was cooled to room temperature and poured into 300 mL of 3 N aqueous hydrochloric acid. The aqueous phase was extracted with 200 mL of dichloromethane and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residual oil was distilled at 0.2–0.5 mm to give 20.5 g of material boiling from 55 to 65 °C. This material was recrystallized from 25 mL of hexane at low temperature to afford 14.3 g of enone **5** (mp 45–47 °C). The colorless mother liquor, which contained a mixture of **5**, the cis isomer, and butadiene oligomers, was dissolved in 25 mL of dichloromethane containing 0.5 g of sodium methoxide and stirred at room temperature for 24 h. The mixture was washed with two 25-mL portions of water, dried (Na_2SO_4), bulb to bulb distilled, and recrystallized from hexane to give an additional 2.5 g (16.8 g total, 70%) of enone **5**: IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 1.2–2.7 (m, 12 H), 5.60 (m, 2 H, =CH); exact mass calcd for $C_{10}H_{14}O$ m/e 150.1044, found m/e 150.1047.

***rel*-(1*S*,4a*S*,8a*S*)-1,2,3,4,4a,5,8,8a-Octahydronaphthalen-1-ol (6).** To a slurry of 7.6 g (0.2 mol) of lithium aluminum hydride in 400 mL of tetrahydrofuran cooled in a dry ice–acetone bath was added a solution of 56.0 g (0.36 mol) of enone **5** in 200 mL of tetrahydrofuran over a 75-min period. The cold bath was removed and the mixture was stirred for an additional 3 h followed by sequential addition of 7.0 mL of water, 7.0 mL of 3 N aqueous sodium hydroxide, 14.0 mL of water, and 200 mL of ether. The mixture was filtered and the filter cake was rinsed with 200 mL of tetrahydrofuran. The filtrates were concentrated in vacuo. The residual oil was dissolved in 200 mL of hexane and crystallized to give 25.0 g of alcohol **6**. A second crystallization from 70 mL of hexane afforded a second crop of 15.9 g of **6**. The orange mother liquor was chromatographed over 150 g of silica gel (ethyl acetate–hexane, 1:9) to give 5.1 g (9%) of alcohol **7**: IR (CCl_4) 3630, 3300 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.4 (m, 12 H), 2.5 (s, 1 H, OH), 3.7 (m, 1 H, OCH), 5.5 (m, 2 H, =CH); mass spectrum, m/e 152 (P^+, weak), 134 ($P - H_2O$). An additional 6.4 g of **6** was obtained (47.3 g total, 83%) after crystallization from hexane: mp 64–67 °C; IR (CCl_4) 3630, 3450 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.7 (m, 13 H), 3.23 (m, 1 H, OCH), 5.70 (m, 2 H, =CH); exact mass calcd for $C_{10}H_{16}O$ m/e 152.1201, found m/e 152.1204.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.14; H, 10.37.

***N*-[*rel*-(1*R*,4a*S*,8a*S*)-1,2,3,4,4a,5,8,8a-Octahydronaphthyl]succinimide (8).** To a stirred solution of 47.3 g (0.31 mol) of alcohol **6**, 81.2 g (0.31 mol) of triphenylphosphine, and 33.4 g (0.34 mol) of succinimide in 1.0 L of tetrahydrofuran cooled in an ice-water bath was added over a 45-min period 53.9 g (0.31 mol) of diethyl azodicarboxylate. The solution was stirred at room temperature for 30 min and concentrated in vacuo. The resulting mixture was suspended in 600 mL of ethyl acetate–hexane (5:2) and the resulting solids (113 g) were removed by filtration. The filter cake was rinsed with 100 mL of ethyl acetate–hexane (5:2) and the combined filtrates were concentrated in vacuo. The residual orange liquid was chromatographed over 700 g of silica gel (ethyl acetate–hexane, 1:2). Fractions containing the desired imide **8** and alcohol **7** were concentrated. Alcohol **7** was removed by distillation at 85–105 °C and 0.7 mm to leave 49.0 g (62%) of imide **8**, suitable for use in subsequent reactions: IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 0.9–2.35 (m, 11 H), 2.57 (s, 4 H, $C(O)CH_2$), 4.40 (broad s, 1 H, NCH), 5.49 (m, 2 H, =CH); exact mass calcd for $C_{14}H_{19}NO_2$ m/e 233.1415, found m/e 233.1421.

***N*-[*rel*-(1*R*,2*S*,3*S*)-2,3-Bis(2-hydroxyethyl)cyclohexyl]succinimide (9).** Through a solution of 11.0 g (47.2 mmol) of imide **8** in 200 mL of methanol cooled in a dry ice–acetone bath was passed over a 43-min period 51.6 mmol of ozone. To the resulting solution was added over a 10-min period 1.79 g (47.2 mmol) of sodium borohydride. The cold bath was removed and the progress of the reaction was followed by TLC analysis (silica gel; ethyl acetate–methanol, 9:1) of aliquots taken at 5-min intervals. When the amount of the desired product was at a maximum and more polar side products began to appear, the mixture was diluted with 300 mL of saturated brine and extracted with seven 300-mL portions of dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual white solid was slurried in 25 mL of ethyl acetate, collected, and dried to give 10.2 g (81%) of the desired diol, **9**, as a white solid: mp 120–122 °C; IR ($CHCl_3$) 3620, 3340, 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.23 (m, 12 H), 2.63 (s, 4 H, $C(O)CH_2$), 2.97 (broad s, 2 H, OH), 3.67 (m, 2 H, CH_2O), 4.22 (dt, J = 13, 4 Hz, 1 H, NCH); exact mass calcd for $C_{14}H_{23}NO_4$ m/e 269.1627, found m/e 269.1633.

***N*-[*rel*-(1*R*,2*S*,3*S*)-2,3-Divinylcyclohexyl]succinimide (10).** To a solution of 30.5 g (0.113 mol) of diol **9** and 68.1 g (0.3 mol) of *o*-nitrophenyl selenocyanate in 700 mL of tetrahydrofuran cooled in an ice-water bath was added over a 15-min period 60.6 g (0.3 mol) of tri-*n*-butylphosphine. The cooling bath was removed and the mixture was stirred at room temperature for 45 min. The resulting solution was cooled in an ice water bath and 225 mL of 30% aqueous hydrogen peroxide was added over a 20-min period. The cooling bath was removed and the mixture was stirred for an additional 3 h while being monitored by TLC. The solution was poured into 1.5 L of dichloromethane, washed with 1.0 L of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residual black liquid was chromatographed twice over 750 g of silica gel (ethyl acetate–hexane, 1:2) to give 20.1 g (76%) of diene **10** as a pale yellow oil: IR (CCl_4) 1708 cm^{-1}; NMR (C_6D_6) δ 1.2–1.70 (m, 5 H), 1.74 (s, 4 H, $COCH_2$), 2.53 (broad s, 1 H, =CC(3)H), 2.65 (qu, 1 H, =CC(2)H), 2.78 (m, 1 H, C(6)H), 4.45 (dt, J = 12, 4.5 Hz, 1 H, NCH), 4.89 (d with fine coupling, J = 16 Hz, 1 H, C(2)C=CH), 4.99 (dd, J = 10, 2 Hz, 1 H, C(2)C=CH), 5.15 (dt, J = 11, 2 Hz, 1 H, C(3)C=CH), 5.35 (dt, J = 17, 2 Hz, 1 H, C(3)C=CH), 5.90 (octet, 1 H, C(3)CH=), 6.34 (octet, 1 H, C(2)CH=); exact mass calcd for $C_{14}H_{19}NO_2$ m/e 233.1415, found m/e 233.1408.

***N*-[*rel*-(1*R*,2*S*,3*S*)-2,3-Divinylcyclohexyl]-5-hydroxy-2-pyrrolidinone (11).** To 6.5 g (29.7 mmol) of imide **10** in 100 mL of dry toluene cooled to −70 °C was added diisobutylaluminum hydride (25 wt % in toluene) at a rate such that the reaction temperature did not exceed −65 °C. The reaction progress was followed by TLC analysis (silica gel, ethyl acetate) of aliquots taken directly from the reaction mixture. After 34 mL of the diisobutylaluminum hydride solution had been added (30 min), the cold mixture was poured into a vigorously stirred mixture of 300 mL of dichloromethane and 200 mL of 5% aqueous sulfuric acid. The organic phase was dried (Na_2SO_4), concentrated in vacuo, and the residual oil was chromatographed over 120 g of silica gel (ethyl acetate) to give 5.2 g (80%) of carbinolamide **11** as a solid mixture of diastereomers: mp 62–77 °C; IR (CCl_4) 3640, 3380, 1690, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.95 (m, 12 H), 3.30 (d, J = 7 Hz, 0.5 H, OH), 4.00–4.46 (m, 1.5 H, NCH and OH), 4.83–5.43 (m, 5 H, $=CH_2$ and NCHO), 5.73–6.52 (m, 2 H, =CH); exact mass calcd for $C_{14}H_{21}NO_2$ m/e 235.1572, found m/e 235.1566.

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 8.99. Found: C, 71.29; H, 9.06.

***rel*-(3a*R*,5*S*,5a*S*,6*S*,9a*R*)-5-(Formyloxy)-1-oxo-6-vinyldodecahydropyrrolo[1,2-*a*]quinoline (13).** To 230 mL of 98% formic acid was added over a 15-min period with cooling in an ice water bath a solution of 11.5 g (49.0 mmol) of carbinolamide **11** in 40 mL of dichloromethane. The cold bath was removed and the mixture was stirred for 30 min. Most of the formic acid was removed in vacuo and the residue was poured into 500 mL of saturated aqueous sodium bicarbonate. The mixture was stirred for 5 min and extracted with two 200-mL portions of dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. To the residual oil was added 68 mL of hexane–ethyl acetate (50:18) to afford 8.05 g of the desired formate **13**. The mother liquor was chromatographed over 100 g of silica gel (ethyl acetate) to give an additional 2.05 g (10.1 g total, 79%) of formate **13**: mp 116–119 °C; IR ($CHCl_3$) 1720, 1670 cm^{-1}; NMR (C_6D_6) δ 0.7–2.15 (m, 13 H), 2.50 (broad s, 1 H, CH), 2.96 (nine line m, 1 H, NC(3)H), 4.51 (dt, J = 13, 5 Hz, 1 H, NC(9a)H), 5.00 (qu, 1 H, terminal =CH), 5.07 (dt, J = 11,

2 Hz, 1 H, terminal =CH), 5.19 (td, J = 11, 4 Hz, 1 H, OCH), 5.77 (septet, 1 H, =CH), 7.65 (s, 1 H, CHO); exact mass calcd for $C_{15}H_{21}NO_3$ m/e 263.1521, found m/e 263.1515.

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04. Found: C, 68.52; H, 8.03. In addition 0.13 g (1%) of alcohol **14** and 0.44 g of an unidentified formate were obtained.

***rel*-(3a*R*,5*S*,5a*S*,6*S*,9a*R*)-5-Hydroxy-1-oxo-6-vinyldodecahydropyrrolo[1,2-*a*]quinoline (14) and *rel*-(3a*R*,5*S*,5a*S*,6*S*,9a*R*)-1-Oxo-6-vinyldodecahydropyrrolo[1,2-*a*]quinol-5-yl *S*-Methyl Dithiocarbonate (15).** To a solution of 10.0 g (38.0 mmol) of formate **13** in 100 mL of methanol was added in a single portion 17 mL (51.0 mmol) of 3 N aqueous sodium hydroxide. The mixture was stirred at room temperature for 5 min, diluted with 150 mL of water, and extracted with three 200-mL portions of dichloromethane. The extracts were dried (Na_2SO_4) and concentrated in vacuo to give 8.9 g (100%) of alcohol **14** as a white solid: mp 102–104 °C; IR (CCl_4) 3630, 3380, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.66 (m, 13 H), 3.01 (m, 2 H, =CCH and OH), 3.47–4.50 (m, 3 H, NCH and OCH), 4.93–5.29 (m, 2 H, $=CH_2$), 5.73–6.29 (m, 1 H, =CH); exact mass calcd for $C_{14}H_{21}NO_2$ m/e 235.1572, found m/e 235.1579.

To a suspension of 1.37 g (57.0 mmol) of sodium hydride in 100 mL of tetrahydrofuran was added in a single portion a solution of the alcohol obtained above in 150 mL of tetrahydrofuran. To the mixture was added 60 mg of imidazole followed by warming at 60 °C for 1 h. To the warm solution was carefully added 15 mL (248 mmol) of carbon disulfide followed by warming for 5 min. To the resulting mixture was added 15 mL (241 mmol) of iodomethane, and warming was continued for another 5 min. The mixture was poured into 1.0 L of water–dichloromethane (1:1). The aqueous phase was extracted with 200 mL of dichloromethane, and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residual yellow solid was recrystallized from 140 mL of ethyl acetate–hexane (60:80) to give 9.0 g of xanthate **15**. Two additional crops gave another 2.3 g (11.3 g total, 91%) of **15**: mp 145–147 °C; IR ($CHCl_3$) 1675, 1425 cm^{-1}; NMR ($CDCl_3$) δ 1.07–2.60 (m, 14 H), 2.60 (s, 3 H, SCH_3), 3.80 (m, 1 H, NCH), 4.40 (m, 1 H, NCH), 4.97–5.23 (m, 2 H, $=CH_2$), 5.95 (m, 1 H, =CH), 6.12 (td, J = 8, 3 Hz, 1 H, OCH); exact mass calcd for $C_{16}H_{23}NO_2S_2$ m/e 325.1170, found m/e 325.1160.

Anal. Calcd for $C_{16}H_{23}NO_2S_2$: C, 59.04; H, 7.12. Found: C, 59.25; H, 7.11.

***rel*-(3a*S*,5a*S*,6*S*,9a*R*)-1-Oxo-6-vinyldodecahydropyrrolo[1,2-*a*]quinoline (16).** To a solution of 19.8 g (68.0 mmol) of tri-*n*-butyltin hydride in 240 mL of toluene under reflux was added over a 45-min period a solution of 11.0 g (34.0 mmol) of xanthate **15** in 160 mL of toluene. The solution was warmed under reflux for 16 h, concentrated in vacuo, and chromatographed over 350 g of silica gel (ethyl acetate–hexane, 3:1, followed by ethyl acetate) to give 5.05 g (68%) of lactam **16** as a white crystalline solid: mp 46–50 °C; IR (CCl_4) 1670 cm^{-1}; NMR (CCl_4) δ 1.0–2.5 (m, 16 H), 3.4 (m, 1 H, C(3a)H), 4.08 (m, 1 H, C(9a)H), 4.8–5.2 (m, 2 H, $=CH_2$), 6.0 (eight-line m, 1 H, =CH); exact mass calcd for $C_{14}H_{21}NO$ m/e 219.1881, found m/e 219.1885.

***N*-[*rel*-(1*R*,2*S*,3*S*)-2,3-Divinylcyclohexyl]-5-thiophenoxy-2-pyrrolidinone (17).** A mixture of 222 mg (5.87 mmol) of sodium borohydride and 490 mg (2.10 mmol) of imide **10** in 13 mL of absolute ethanol was cooled in an ice water bath under argon. Over a period of 3.5 h, three to four drops of 1.6 N ethanolic hydrochloric acid were added at 5-min intervals. The mixture was adjusted to pH 3 with 1.6 N ethanolic hydrochloric acid and stirred at 0 °C for another 30 min. The mixture was then adjusted to pH 9 with a solution of 1% ethanolic potassium hydroxide. The temperature was maintained below 5 °C throughout the entire process. The resulting mixture was partitioned between 25 mL of water and 50 mL of dichloromethane. The aqueous phase was extracted with three 25-mL portions of dichloromethane, and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residual oil (519 mg) was stirred with 2.3 mL of thiophenol and 19.2 mg (0.1 mmol) of *p*-toluenesulfonic acid monohydrate for 30 min under argon. The mixture was partitioned between 30 mL of dichloromethane and 27 mL of 1 N aqueous sodium hydroxide. The aqueous phase was extracted with two 30-mL portions of dichloromethane, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residual yellow oil (621 mg) was first chromatographed over 20 g of silica gel (eluted with ethyl acetate–hexane, 13:87) and then over a Lobar size B column (eluted with ethyl acetate–hexane, 1:9) to afford 419 mg (61%) of the least polar and major diastereomer of **17** as pale yellow crystals: mp 92–94 °C; IR (CCl_4) 1690 cm^{-1}; NMR (CCl_4) δ 1.50–2.90 (m, 12 H, CH_2 manifold), 4.15–4.50 (m, 1 H, NCH), 4.90–5.48 (m, 5H, $=CH_2$ and SCHN), 5.72–6.50 (m, 2 H, =CH), 7.15–7.50 (m, 5 H, ArH); mass spectrum, m/e (relative intensity) 218 (M^+ – SPh, 100), 217 (5), 135 (5), 134(5), 124 (5), 110 (15), 109 (10), 93 (15), 91 (8), 84 (40).

Further elution gave 27 mg (4%) of the minor diastereomer of **17** as a light yellow solid: mp 72.5–74.5 °C; IR (CCl_4) 1700 cm^{-1}; NMR (CCl_4) δ 1.30–3.00 (m, 12 H, CH_2 manifold), 3.70 (td, J = 11, 3 Hz, 1 H, NCH), 4.70–5.20 (m, 5 H, $=CH_2$ and SCHN), 5.60 (m, 2 H, =CH), 7.15–7.50 (m, 5 H, ArH); mass spectrum, m/e (relative intensity) 218 (M^+ – SPh), 217 (7), 134 (11), 110 (29), 93 (14), 84 (41).

Continued elution gave 68 mg (12%) of recovered imide **10**.

Cyclization of Thiophenoxy Lactam 17 to 16 and 18. To a solution of 398 mg (1.22 mmol) of the major diastereomer of **17** in 16 mL of dry benzene warmed under argon at 80 °C was added dropwise over a 100-min period a solution of 0.4 mL (1.52 mmol) of tri-*n*-butyltin hydride and 12 mg (0.07 mmol) of AIBN in 11 mL of benzene. The resulting solution was warmed at 80 °C for 2 h, cooled to room temperature, and concentrated in vacuo. The residual yellow oil (866 mg) was chromatographed first over 40 g of silica gel (eluted with ethyl acetate–hexane, 55:45) and then over a Lobar size A column to give 136 mg (51%) of **18** as a pale yellow oil: IR (CCl_4) 1690 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (d, J = 6 Hz, 3 H, CH_3), 1.09–1.40 (m, 3 H), 1.46–2.17 (m, 8 H), 2.38 (ddd, J = 16, 9, 3 Hz, 1 H, COCH), 2.74 (ddd, J = 16, 11.7, 8.6 Hz, COCH), 3.92 (q, J = 5 Hz, 1 H, pyrrolizidinone angular NCH), 4.22 (td, J = 9, 6.5 Hz, 1 H, NCH), 4.98–5.07 (m, 2 H, $=CH_2$), 5.78 (ddd, J = 17, 9, 8 Hz, 1 H, =CH); exact mass calcd for $C_{14}H_{21}NO$ m/e 219.1623, found m/e 219.1615.

Continued elution afforded 83 mg (31%) of lactam **16**, which was identical in all respects to the material prepared via the *N*-acyliminium ion route.

***rel*-(3a*S*,5a*S*,6*S*,9a*R*)-1-Thioxo-6-vinyldodecahydropyrrolo[1,2-*a*]quinoline (19).** A mixture of 1.0 g (4.57 mmol) of lactam **16** and 0.93 g (2.30 mmol) of Lawesson's reagent in 20 mL of toluene was warmed with an oil bath at 100 °C for 10 min. The solution was cooled to room temperature and chromatographed directly over 80 g of silica gel (ethyl acetate–hexane, 1:1) to afford 1.02 g (95%) of thiolactam **19** as a white solid: mp 85–89 °C; IR (CCl_4) 1640 (w), 1470 cm^{-1}; NMR ($CDCl_3$) δ 1.03–2.50 (m, 14 H), 2.94 (m, 2 H, $C(S)CH_2$), 3.87 (m, 1 H, NCH), 4.84–5.27 (m, 3 H, $=CH_2$ and NCH), 6.03 (octet, 1 H, =CH); exact mass calcd for $C_{14}H_{21}NS$ m/e 235.1394, found m/e 235.1388.

***rel*-(3a*S*,5a*S*,6*S*,9a*R*)-1(*E*)-(Carbethoxymethylidene)-6-vinyldodecahydropyrrolo[1,2-*a*]quinoline (20).** A mixture of 1.02 g (4.34 mmol) of thiolactam **19** and 0.90 g (5.42 mmol) of ethyl bromoacetate in 15 mL of ether was stirred at room temperature for 46 h. The solvent was removed in vacuo and the resulting oil was dissolved in 15 mL of dichloromethane. To the stirred solution was added, with cooling in an ice water bath, a mixture of 1.31 g (5.0 mmol) of triphenylphosphine and 1.01 g (10.0 mmol) of triethylamine in 5.0 mL of dichloromethane. The mixture was stirred for 15 min and concentrated in vacuo. The residue was chromatographed directly over 80 g of silica gel (ethyl acetate–hexane, 1:9) to give the desired product contaminated by some triphenylphosphine sulfide. This material was recrystallized from 20 mL of ethyl acetate–hexane (1:9) to afford 1.08 g (86%) of vinylogous urethane **20** (mp 87–95 °C) contaminated by only trace amounts of triphenylphosphine sulfide. A small sample was recrystallized to give analytically pure material: mp 99–101 °C; IR ($CHCl_3$) 1670, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.2 [m with t (J = 7 Hz) at 1.26, 18 H], 2.35 (m, 1 H, C(6)H), 2.73 (m, 1 H, C(2)H), 3.40 (m, 2 H, C(2)H and NCH), 3.75 (m, 1 H, NCH), 4.64 (s, 1 H, $CHCO_2Et$), 5.04–5.16 (m, 2 H, $=CH_2$), 5.96 (m, 1 H, =CH); exact mass calcd for $C_{18}H_{27}NO_2$ m/e 289.2041, found m/e 289.2034.

Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.69; H, 9.40. Found: C, 74.72; H, 9.36.

Ethyl α-*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-Vinyldodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (21) and Ethyl α-*rel*-(1*R*,3a*S*,5a*S*,6*S*,9a*R*)-6-Vinyldodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (22). To a solution of 289 mg (1.0 mmol) of vinylogous urethane **20** in 5.0 mL of methanol was added a trace of bromocresol green followed by 63 mg (1.0 mmol) of sodium cyanoborohydride. A solution of 2.1 M methanolic hydrochloric acid was added dropwise to maintain a pH of 4 (yellow end point). After 0.63 mL of the acid had been added, the solution remained yellow. The mixture was stirred for 30 min and concentrated in vacuo. The residual material was chromatographed twice over silica gel (30 g and 12 g; chloroform–methanol–aqueous NH_4OH, 960:36:4) to afford 173 mg (59%) of amino ester **21**: IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.80 [m with t (J = 7 Hz) at 1.27, dd (J = 14, 9 Hz) at 2.20, dd (J = 14, 4 Hz) at 2.67, 22 H, CH_3 and CH_2CO_2Et], 3.12 (m, 2 H, NCH), 4.14 (q, J = 7 Hz, 2 H, OCH_2), 4.90–5.20 (m, 2 H, $=CH_2$), 5.97 (octet, 1 H, =CH); exact mass calcd for $C_{18}H_{29}NO_2$ m/e 291.2198, found m/e 291.2205; 20 mg (7%) of a mixture of amino esters **21** and **22**, and 84 mg (29%) of amino ester **22**: IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.50 [m with t (J = 7 Hz) at 1.27, 20 H, CH_3], 2.55 (dd, J = 14, 4 Hz, 1 H, $CHCO_2Et$), 2.83 (m, 1 H, NCH), 3.27 (m, 1 H, NCH), 3.44 (m, 1 H, NCH), 4.13 (q, J = 7 Hz, 2 H, OCH_2), 4.95–5.20

(m, 2 H, $=CH_2$), 5.93 (octet, 1 H, =CH); exact mass calcd for $C_{18}H_{29}NO_2$ *m/e* 291.2198, found *m/e* 291.2205.

2-[*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-Vinyldodecahydropyrrolo[1,2-*a*]quinol-1-yl]ethanol (23). To 160 mg (0.55 mmol) of amino ester **21** in 5 mL of tetrahydrofuran was added 40 mg (1.1 mmol) of solid lithium aluminum hydride. The mixture was stirred at room temperature for 60 min followed by the addition of two drops of water, two drops of 3 N aqueous sodium hydroxide, two drops of water, 5 mL of tetrahydrofuran, and some magnesium sulfate. The mixture was filtered and concentrated in vacuo to afford 122 mg (90%) of carbinolamine **23** as a pale yellow oil, homogeneous by TLC (alumina; ethyl acetate–hexane, 3:7): IR ($CHCl_3$) 3250 (broad), 1630 (w) cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.85 (m, 19 H), 3.0–4.18 (m, 4 H, NCH and OCH_2), 4.85–5.35 (m, 3 H, $=CH_2$ and OH), 6.00 (octet, 1 H, =CH); exact mass calcd for $C_{16}H_{27}NO$ *m/e* 249.2092, found *m/e* 249.2089.

2-[*rel*-(1*R*,3a*S*,5a*S*,6*S*,9a*R*)-6-Vinyldodecahydropyrrolo[1,2-*a*]quinol-1-yl]ethanol (24). A solution of 70 mg (0.24 mmol) of amino ester **22** was treated with 40 mg (1.1 mmol) of lithium aluminum hydride as described above for **21** to afford 60 mg (97%) of amino alcohol **24** as a pale yellow oil, homogeneous by TLC (alumina; ethyl acetate–hexane, 3:7): IR ($CHCl_3$) 3250 (broad), 1630 (w) cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.65 (m, 18 H), 2.8–4.25 (m, 5 H, NCH and OCH_2), 4.87–5.22 (m, 2 H, $=CH_2$), 5.87 (octet, 1 H, =CH), 6.40 (broad s, 1 H, OH); exact mass calcd for $C_{16}H_{27}NO$ *m/e* 249.2092, found *m/e* 249.2100.

2-[*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-Vinyldodecahydropyrrolo[1,2-*a*]quinol-1-yl]ethyl *tert*-Butyldiphenylsilyl Ether (25). A solution of 100 mg (0.4 mmol) of amino alcohol **23**, 213 mg (0.81 mmol) of *tert*-butylchlorodiphenylsilane, and 53 mg (0.8 mmol) of imidazole in 1.0 mL of *N,N*-dimethylformamide was allowed to stand at room temperature for 36 h. The *N,N*-dimethylformamide was removed in vacuo. The residue was suspended in ethyl acetate and chromatographed over 15 g of alumina (activity III; ethyl acetate–hexane, 1:9) to give 190 mg (100%) of the desired product as a colorless oil: IR (CCl_4) 1430 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.56 (m with s at 1.07, 28 H, CH_3), 2.78 (m, 1 H, NCH), 3.13 (m, 1 H, NCH), 3.70 (t, *J* = 6 Hz, 2 H, OCH_2), 4.89–5.20 (m, 2 H, $=CH_2$), 5.99 (octet, 1 H, =CH), 7.35 (m, 6 H, Ar H), 7.67 (m, 4 H, Ar H); mass spectrum, *m/e* 487 (P^+, weak).

2-[*rel*-(1*R*,3a*S*,5a*S*,6*S*,9a*R*)-6-Vinyldodecahydropyrrolo[1,2-*a*]quinol-1-yl]ethyl *tert*-Butyldiphenylsilyl Ether (26). A solution of 55 mg (0.22 mmol) of amino alcohol **24**, 120 mg (0.45 mmol) of *tert*-butylchlorodiphenylsilane, and 34 mg (0.5 mmol) of imidazole in 0.4 mL of *N,N*-dimethylformamide was allowed to stand at room temperature for 36 h. Workup and purification as described above for **25** gave 98 mg (93%) of silyl ether **26**: IR (CCl_4) 1430 cm^{-1}; NMR (CCl_4) δ 0.95–2.35 (m with s at 1.07, 27 H, CH_3), 2.77 (m, 1 H, NCH), 3.13 (m, 2 H, NCH), 3.67 (broad t, *J* = 6 Hz, 2 H, OCH_2), 4.87–5.15 (m, 2 H, $=CH_2$), 5.83 (octet, 1 H, =CH), 7.33 (m, 6 H, Ar H), 7.61 (m, 4 H, Ar H).

2-[*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-(β-Hydroxyethyl)-dodecahydropyrrolo[1,2-*a*]quinol-1-yl]ethyl *tert*-Butyldiphenylsilyl Ether (27). To a solution of 0.4 mmol of disiamylborane (prepared from 0.4 mmol of borane–tetrahydrofuran complex and 0.8 mmol of 2-methyl-2-butene) in 1.3 mL of tetrahydrofuran cooled in an ice water bath was added 190 mg (0.4 mmol) of olefin **25**. The cooled mixture was stirred for 30 min followed by the sequential addition of 0.133 mL (0.4 mmol) of 3 N aqueous sodium hydroxide and 0.133 mL (1.2 mmol) of 30% aqueous hydrogen peroxide. The mixture was stirred at room temperature for 30 min and diluted with 3.0 mL of tetrahydrofuran. A spatula tip full of sodium chloride was added: the tetrahydrofuran solution was decanted, and the residual solids were rinsed with 3.0 mL of tetrahydrofuran. The combined tetrahydrofuran solutions were concentrated and chromatographed over 20 g of alumina (activity III; ethyl acetate–hexane, 1:9 progressing to 1:1) to give 126 mg (63%) of alcohol **27** as a colorless oil which solidified upon standing for several weeks in the refrigerator: mp 95–102 °C; IR (CCl_4) 3640, 3250, 1435 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.6 (m with s at 1.07, 31 H, CH_3), 2.78 (m, 1 H, NCH), 3.18 (m, 1 H, NCH), 3.70 (four-line m, 4 H, OCH_2), 7.40 (m, 6 H, Ar H), 7.70 (m, 4 H, Ar H); exact mass calcd for $C_{32}H_{47}NO_2Si$ *m/e* 505.3376, found *m/e* 505.3383.

2-[*rel*-(1*R*,3a*S*,5a*S*,6*S*,9a*R*)-6-(2-Hydroxyethyl)dodecahydropyrrolo[1,2-*a*]quinol-1-yl]ethyl *tert*-Butyldiphenylsilyl Ether (28). To a solution of 0.25 mmol of disiamylborane in 1.0 mL of tetrahydrofuran was added over a 3 min period with cooling in an ice water bath 98 mg (0.2 mmol) of olefin **26** in 1.0 mL of tetrahydrofuran. The resulting solution was stirred for 30 min, treated with 0.083 mL of 3 N aqueous sodium hydroxide and 0.082 mL of 30% aqueous hydrogen peroxide, and worked up as described above for **27** to afford 49 mg (50%) of alcohol **28** as a colorless oil: IR ($CHCl_3$) 3620, 1430 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.40 (m with s at 1.07, 30 H, CH_3), 2.66–3.36 (m, 3 H, NCH), 3.67 (complex m, 4 H, OCH_2), 7.40 (m, 6 H, Ar H), 7.67 (m, 4 H, Ar H); exact mass calcd for $C_{32}H_{47}NO_2Si$ *m/e* 505.3376, found *m/e* 505.3388.

***rel*-(3a*S*,5a*S*,6*S*,9a*R*)-1(*E*)-(Carbethoxymethylidene)-6-(2-hydroxyethyl)dodecahydropyrrolo[1,2-*a*]quinoline (29).** To a solution of 2.0 mmol of disiamylborane (prepared from 2.0 mmol of borane–tetrahydrofuran complex and 4.0 mmol of 2-methyl-2-butene) in 6.0 mL of tetrahydrofuran cooled in an ice-water bath was added over a 5-min period 578 mg (2.0 mmol) of olefin **20** in 5 mL of tetrahydrofuran. The cooled mixture was stirred for 45 min followed by sequential addition of 0.67 mL (2.0 mmol) of 3 N aqueous sodium hydroxide and 0.67 mL (2.0 mmol) of 30% aqueous hydrogen peroxide. The resulting mixture was stirred at room temperature for 30 min and diluted with 10 mL of tetrahydrofuran. A small portion of sodium chloride was added and the tetrahydrofuran solution was decanted. The residual solid was rinsed with two 10-mL portions of tetrahydrofuran. The combined tetrahydrofuran solutions were concentrated in vacuo, and the residual colorless oil was chromatographed over 60 g of silica gel (ethyl acetate–hexane, 1:1) to afford 480 mg (78%) of alcohol **29** as an oil which crystallized on standing: mp 82–84 °C (ethyl acetate–hexane); IR (CCl_4) 3630, 3300, 1685, 1590 cm^{-1}; NMR (CCl_4) δ 0.9–2.3 [m with t (*J* = 7 Hz) at 1.23, 19 H, CH_3], 2.62 (dt, *J* = 16, 9 Hz, 1 H, =CCH), 2.99 (s, 1 H, OH), 3.07–3.78 (m, 5 H, =CCH, NCH and OCH_2), 3.93 (q, *J* = 7 Hz, 2 H, OCH_2), 4.35 (s, 1 H, =CH); exact mass calcd for $C_{18}H_{29}NO_3$ *m/e* 307.2147, found *m/e* 307.2155.

***rel*-(3a*S*,5a*S*,6*S*,9a*R*)-1(*E*)-(Carbethoxymethylidene)-6-((2-*tert*-butyldiphenylsiloxy)ethyl)dodecahydropyrrolo[1,2-*a*]quinoline (30).** A solution of 404 mg (1.31 mmol) of alcohol **29**, 0.75 mL (3.0 mmol) of *tert*-butylchlorodiphenylsilane, and 272 mg (4.0 mmol) of imidazole in 4.0 mL of *N,N*-dimethylformamide was allowed to stand at room temperature for 60 min. The solvent was removed in vacuo and the residue was chromatographed over 25 g of silica gel (ethyl acetate–hexane, 1:5) to afford 680 mg (95%) of ether **30** as a white solid: mp 132–134 °C; IR (CCl_4) 1735, 1640, 1480 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.4 [m with s at 1.07 and t (*J* = 7 Hz) at 1.27, 28 H, CH_3], 2.74 (dt, *J* = 16, 9 Hz, 1 H, =CCH), 3.20–3.85 (m, 5 H, =CCH, NCH, and OCH_2), 4.13 (q, *J* = 7 Hz, 2 H, OCH_2), 4.56 (s, 1 H, =CH), 7.40 (m, 6 H, ArH), 7.68 (m, 4 H, Ar H); exact mass calcd for $C_{34}H_{47}NO_3Si$ *m/e* 545, found *m/e* 545.

Ethyl α-*rel*-(1*R*,3a*S*,5a*S*,6*S*,9a*R*)-6-(2-Hydroxyethyl)dodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (32). To a solution of 0.25 mmol of disiamylborane in 0.9 mL of tetrahydrofuran was added with cooling in an ice-water bath 58 mg (0.2 mmol) of olefin **22** in 0.6 mL of tetrahydrofuran. The solution was stirred for 30 min at room temperature followed by sequential addition of 0.083 mL (0.25 mmol) of 3 N aqueous sodium hydroxide and 0.083 mL (0.75 mmol) of 30% aqueous hydrogen peroxide. The mixture was worked up as described above for **27** and the crude product was chromatographed over 12 h of alumina (activity III; ethyl acetate–hexane, 2:1) to give 36 mg (58%) of hydroxy ester **32** as a colorless oil: IR (CCl_4) 3630, 3450, 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.66 [m with t (*J* = 7 H) at 1.27, dd (*J* = 15, 9 Hz) at 2.23, dd (*J* = 15, 4 Hz) at 2.53, 24 H, CH_3 and CH_2CO_2Et], 2.81 (m, 1 H, NCH), 3.33 (m, 2 H, NCH), 3.67 (t, *J* = 6 Hz, 2 H, OCH_2), 4.13 (q, *J* = 7 Hz, 2 H, OCH_2); exact mass calcd for $C_{18}H_{31}NO_3$ *m/e* 309.2303, found *m/e* 309.2295.

Ethyl α-*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-(2-Hydroxyethyl)dodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (31). To a solution of 0.4 mmol of disiamylborane in 1.3 mL of tetrahydrofuran was added 105 mg (0.36 mmol) of olefin **21** in 1.0 mL of tetrahydrofuran over a 3 min period with cooling in an ice water bath. The solution was stirred for 30 min at room temperature followed by sequential addition of 0.133 mL (0.4 mmol) of 3 N aqueous sodium hydroxide and 0.132 mL (1.2 mmol) of aqueous hydrogen peroxide. The mixture was worked up as described above for **27**, and the crude product was chromatographed over 12 g of alumina (activity III, ethyl acetate) to give 68 mg (61%) of hydroxy ester **31** as a colorless oil: IR (CCl_4) 3630, 3300, 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.75 [m with t (*J* = 7 Hz) at 1.27, dd (*J* = 15, 9 Hz) at 2.18, dd (*J* = 15, 4.5 Hz) at 2.67, 25 H, CH_3 and CH_2CO_2Et], 3.10 (m, 2 H, NCH), 3.68 (t, *J* = 6 Hz, 2 H, OCH_2), 4.13 (q, *J* = 7 Hz, 2 H, OCH_2); exact mass calcd for $C_{18}H_{31}NO_3$ *m/e* 309.2303, found *m/e* 309.2310.

Ethyl α-*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-[2-(*tert*-Butyldiphenylsiloxy)-ethyl]dodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (33). A mixture of 55 mg (0.145 mmol) of hydroxy ester **31**, 137 mg (0.52 mmol) of *tert*-butylchlorodiphenylsilane, and 37 mg (0.54 mmol) of imidazole in 0.5 mL of *N,N*-dimethylformamide was allowed to stand at room temperature for several hours. The solvent was removed in vacuo and the residue was chromatographed over 10 g of alumina (activity III; ethyl acetate–hexane, 1:9) to give 79 mg (100%) of silyl ether **33** as a colorless oil which crystallized on standing: mp 80–88 °C; IR (CCl_4) 1735 cm^{-1}; NMR (C_6D_6) δ 0.9–2.0 [m with t (*J* = 7 Hz) at 1.03 and s at 1.20, 30 H, CH_3 and *t*-Bu], 2.22 (dd, *J* = 15, 9 Hz, 1 H, $CHCO_2Et$), 2.42 (m, 1 H, C(3)H), 2.60 (dd, *J* = 15, 4.5 Hz, 1 H, $CHCO_2Et$), 3.07 (broad dt, *J*

= 11, 4 Hz, 1 H, C(9a)H), 3.22 (m, 1 H, C(1)H), 3.75 (t, 2 H, OCH_2), 4.00 (q, J = 7 Hz, 2 H, OCH_2), 7.22 (m, 6 H, Ar H), 7.80 (m, 4 H, Ar H); exact mass calcd for $C_{34}H_{49}NO_3Si$ m/e 547.3482, found m/e 547.3498.

Ethyl α-*rel*-(1*R*,3a*S*,5a*S*,6*S*,9a*R*)-6-[2-(*tert*-Butyldiphenylsiloxy)ethyl]dodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (34). A solution of 30 mg (0.1 mmol) of hydroxy ester **32**, 97 mg (0.37 mmol) of *tert*-butylchlorodiphenylsilane, and 0.5 mL of *N,N*-dimethylformamide was allowed to stand at room temperature for several hours. The solvent was removed in vacuo and the resulting residue was chromatographed over 10 g of alumina (activity III; ethyl acetate–hexane, 1:9) to afford 44 mg (81%) of silyl ether **34** as a colorless oil: IR (CCl_4) 1735 cm^{-1}; NMR (C_6D_6) δ 0.8–2.15 [m with t (J = 7 Hz) at 1.00 and s at 1.20, 30 H, CH_3 and *t*-Bu], 2.28 (dd, J = 15, 8 Hz, 1 H, $CHCO_2Et$), 2.49 (dd, J = 15, 4 Hz, 1 H, $CHCO_2Et$), 2.81 (dt, J = 12, 3.5 Hz, 1 H, C(9a)H), 2.14 (broad q, J = 6.5 Hz, 1 H, C(3)H), 3.42 (septet, 1 H, C(1)H), 3.75 (t, 2 H, OCH_2), 4.00 (q, J = 7 Hz, 2 H, OCH_2), 7.28 (m, 6 H, Ar H), 7.80 (m, 4 H, Ar H); mass spectrum, m/e 547 (P^+, weak), 460 (P – CH_2CO_2Et), 291 (P – Ph_2t-BuSiOH).

Preparation of 33 and 34 from Vinylogous Urethane 30. A solution of 230 mg (0.42 mmol) of vinylogous urethane **30** in 8.0 mL of hexane–ethyl acetate (1:1) was hydrogenated at 50 psi over 110 mg of 5% platinum on alumina for 6 h at room temperature. The solution was filtered and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (ethyl acetate) to afford 215 mg (93%) of ester **33** (mp 80–87 °C) and 8 mg (3%) of ester **34**.

Preparation of Hydroxy Ester 31 from 33. To a solution of 279 mg (0.51 mmol) of silyl ether **33** in 1.0 mL of tetrahydrofuran was added 1.53 mL (1.53 mmol) of 1.0 M tetrabutylammonium fluoride in tetrahydrofuran at room temperature. The solution was stirred for 1 h and the tetrahydrofuran was removed in vacuo. The residual pale yellow oil was chromatographed over 25 g of alumina (activity III; ethyl acetate–hexane, 1:4) to afford 145 mg (92%) of alcohol **31** as a colorless oil.

Ethyl α-*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-(2-Oxoethyl)dodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (35) and Ethyl α-*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-(5-Trimethylsilyl-2(*Z*)-penten-4-yn-1-yl)-dodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (36). To a solution of 0.061 mL (0.7 mmol) of oxalyl chloride in 5 mL of dichloromethane was added 0.099 mL (1.39 mmol) of dimethyl sulfoxide at −50 to −55 °C. The mixture was stirred for 5 min, a solution of 96 mg (0.31 mmol) of alcohol **31** in 2 mL of dichloromethane was added at −45 to −55 °C, and the resulting mixture was stirred at −21 °C for 15 min. To the solution was added 0.485 mL (3.48 mmol) of triethylamine. The mixture was stirred at −10 to −20 °C for 5 min followed by stirring at room temperature for 15 min. The resulting suepension was poured into saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated in vacuo. The residual pale yellow oil was chromatographed over 25 g of alumina (activity III; ethyl acetate–hexane, 1:9) to give 74 mg (78%) of aldehyde **35** as an unstable pale yellow oil which was used directly in the next reaction: IR ($CHCl_3$) 1725 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.84 [m with t (J = 7 Hz) at 1.27, 25 H, CH_3], 3.09 (m, 2 H, NCH), 4.08 (q, J = 7 Hz, 2 H, OCH_2), 9.71 (t, J = 2.5 Hz, 1 H, CHO).

To a solution of 51 mg (0.224 mmol) of 1-trimethylsilyl-3-*tert*-butyldimethylsilyl-1-propyne[37] in 2.5 mL of tetrahydrofuran was added 0.125 mL (0.197 mmol) of 1.58 M *tert*-butyllithium in pentane at −64 to −69 °C. The solution was stirred for 1 h at −68 °C, 0.605 mL (0.224 mmol) of 0.37 M magnesium bromide in ether was added, and the resulting colorless solution was stirred at −70 °C for 15 min. To the solution was added 55 mg (0.179 mmol) of aldehyde **35** in 2.0 mL of tetrahydrofuran. The mixture was stirred at −70 °C for 15 min and the cooling bath was removed. The solution was stirred for 30 min, warmed at 50 °C for 30 min, poured into saturated aqueous ammonium chloride, and extracted with dichloromethane. The extracts were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentrated in vacuo. The residual pale yellow oil was chromatographed over 20 g of alumina (activity III; ether–hexane, 1:19) to give 22 mg (30%) of enyne **36** as a colorless oil: IR ($CHCl_3$) 2140, 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.18 (s, 9 H, $SiCH_3$), 1.24 (t, J = 7 Hz, 3 H, CH_3), 1.1–1.95 (m, 16 H), 2.18 (dd, J = 15, 8 Hz, 1 H, $CHCO_2Et$), 2.34 (dt, J = 14, 8 Hz, 1 H, =CCH), 2.51 (m, 1 H, NCH), 2.58 (m, 1 H, =CCH), 2.64 (dd, J = 15, 4.5 Hz, 1 H, $CHCO_2Et$), 3.10 (m, 2 H, NCH), 4.10 (q, J = 7 Hz, 2 H, OCH_2), 5.50 (d, J = 11 Hz, 1 H, =CH), 5.93 (m, 1 H, =CH); exact mass calcd for $C_{24}H_{39}NO_2Si$ m/e 401.2750, found m/e 401.2757. Weak signals at δ 6.2 (m) and 0.16 (s) in the ^1H NMR of this material were attributed to the *E* isomer of **36**.

2-[*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-(5-Trimethylsilyl-2(*Z*)-penten-4-yn-1-yl)dodecahydropyrrolo[1,2-*a*]quinol-1-yl]ethanol (37). To a solution of 18 mg (0.045 mmol) of ester **36** in 2.0 mL of ether was added 0.293 mL (0.45 mmol) of 1.53 M diisobutylaluminum hydride in toluene at −78 °C. The mixture was stirred at −78 °C for 15 min followed by stirring at −20 °C for 30 min. The resulting solution was poured into saturated aqueous sodium chloride, acidified with 1 N aqueous sulfuric acid to pH 3, and extracted with dichloromethane. The combined organic phases were washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residual colorless oil was chromatographed over 20 g of alumina (activity III; ethyl acetate–hexane, 1:9) to give 15 mg (94%) of alcohol **37** as a colorless oil: IR ($CHCl_3$) 3250 (broad), 2140 cm^{-1}; NMR ($CDCl_3$) δ 0.18 (s, 9 H, $SiMe_3$), 0.8–2.4 (m, 18 H), 2.45–3.0 (m, 3 H), 3.0–3.75 (m, 3 H), 3.92 (td, J = 9, 3 Hz, 1 H, C*H*OH), 5.45 (d, J = 11 Hz, 1 H, =CH), 5.85 (m, 1 H, =CH), 6.2 (broad s, 1 H, OH); mass spectrum, m/e 359 (P^+, weak), 314 (P – CH_2CH_2OH).

***dl*-Gephyrotoxin (1).** To a solution of 13 mg (0.036 mmol) of trimethylsilyl enyne **37** in 1.0 mL of *N,N*-dimethylformamide was added 0.36 mL (0.36 mmol) of 1.0 M tetrabutylammonium fluoride in *N,N*-dimethylformamide at room temperature. The solution was stirred for 40 min and the solvent was removed in vacuo. The residual pale yellow oil was chromatographed over 25 g of alumina (activity III; ethyl acetate–hexane, 1:3) to give 11 mg (100%) of gephyrotoxin as a colorless oil which became pale pink upon storage: IR (neat) 3600–3000 (broad), 3300, 2100 cm^{-1}; NMR (C_6D_6) δ 1.00–1.80 (m, methylene and methine manifold), 1.98 (ddt, J = 14.5, 11.5, 4 Hz, 1 H C*H*CH_2OH), 2.28 (m, 1 H, C(3a)H), 2.35 (dt, J = 14, 7 Hz, 1 H, =CHC*H*), 2.66 (dt, J = 14, 8 Hz, 1 H, =CHC*H*), 2.86 (d, J = 2.0 Hz, 1 H, ≡CH), 2.98 (m, 1 H, C(1)H), 3.40 (dt, J = 12, 4.5 Hz, 1 H, C(9a)H), 3.67 (dt, J = 11.5, 4 Hz, 1 H, C*H*OH), 3.97 (td, J = 11.5, 3 Hz, 1 H, C*H*OH), 4.65 (broad s, 1 H, OH), 5.43 (ddt, J = 12, 2.0, 1.0 Hz, 1 H, ≡CCH=), 5.73 (dt with fine coupling, J = 12, 8 Hz, 1 H, =C*H*CH_2); mass spectrum, m/e (relative intensity) 287 (6), 242 (100), 222 (42); exact mass calcd for $C_{19}H_{29}NO$ m/e 287.2249, found m/e 287.2256.

Ethyl α-*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-[2(*S*)-Hydroxy-3(*R*)-(trimethylsilyl)pent-4-en-1-yl]dodecahydropyrrolo[1,2-*a*]quinol-1-yl Acetate (38). A solution of **31** mg (0.101 mmol) of aldehdye **35** and 73 mg (0.304 mmol) of pinacol (*E*)-1-(trimethylsilyl)-1-propene-3-boronate[41] in 1.0 mL of dichloromethane was allowed to stand in the dark for 34 h. To the solution was added 0.606 mL (0.606 mmol) of 1.0 M triethanolamine in dichloromethane. The mixture was stirred for 2 h, poured into saturated aqueous sodium bicarbonate, and extracted with dichloromethane. The combined organic phases were washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and concentreated in vacuo. The residual pale red oil was chromatographed over 25 g of alumina (activity II; ethyl acetate–hexane, 1:9) to afford 42 mg (100%) of β-hydroxysilane **38** as a colorless oil: IR ($CHCl_3$) 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.08, 0.10 (two s, 9 H, $SiMe_3$), 1.00–3.00 [m with t (J = 7 Hz) at 1.27, 26 H], 3.12 (m, 2 H), 3.90 (m, 1 H, NCH), 4.12 (q, J = 7 Hz, 2 H, OCH_2), 4.79–5.16 (m, 2 H, $=CH_2$), 5.46–6.16 (m, 1 H, =CH).

2-[*rel*-(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-[2(*S*)-Hydroxy-3(*R*)-(trimethylsilyl)pent-4-en-1-yl]dodecahydropyrrolo[1,2-*a*]quinol-1-yl]ethanol (39). To a solution of 33 mg (0.078 mmol) of ester **38** in 2.0 mL of ether was added 0.51 mL (0.78 mmol) of 1.53 M diisobutylaluminum, hydride in toluene at −78 °C. The mixture was stirred at −78 °C for 15 min followed by stirring at −20 °C for 30 min. The resulting solution was poured into saturated aqueous sodium chloride, acidified with 1 N aqueous sulfuric acid to pH 3, and extracted with dichloromethane. The combined extracts were washed with satruated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residual colorless oil was chromatographed over 25 g of alumina (activity III; ethyl acetate–hexane, 1:1) to give 25 mg (83%) of diol **39** as a colorless foam: IR ($CHCl_3$) 3300 (broad) cm^{-1}; NMR (C_6D_6) δ 0.17, 0.20 (two s, 9 H, $SiMe_3$), 0.8–3.05 (m, 25 H), 3.3–4.08 (m, 4 H, CH_2O and C(9a)H), 5.03 (m, 2 H, $=CH_2$), 5.82, 6.06 (two dt, J = 15, 9 Hz, 1 H, =CH); exact mass calcd for $C_{22}H_{41}NO_2Si$ m/e 379.2906, found m/e 379.2913.

***dl*-Dihydrogephyrotoxin (2).** To a solution of 22 mg (0.058 mmol) of β-hydroxysilane **39** in 1.0 mL of tetrahydrofuran was added with cooling in an ice bath a suspension of 63 mg (0.58 mmol) of potassium hydride (35% mineral oil dispersion) in 1.0 mL of tetrahydrofuran. The mixture was stirred at room temperature for 30 min, poured into ice-cold saturated aqueous sodium bicarbonate, and extracted with dichloromethane. The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), and concentrated in vacuo. The residual colorless oil was chromatographed over 25 g of alumina (activity III; ethyl acetate–hexane, 3:17) to give 10 mg (60%) of dihydrogephyrotoxin (**2**) as a colorless oil: IR ($CHCl_3$) 3250 (broad) cm^{-1}; NMR ($CDCl_3$) δ 1.04–1.98 (m, 18 H), 2.08 (m, 1 H, C*H*CH_2OH), 2.22 (m, 1 H, =CCH), 2.53 (m, 2 H, =CCH and NCH), 3.30 (m, 2 H, NCH), 3.66 (dt, J = 12, 4 Hz, 1 H, C*H*OH), 4.04 (td, J = 12, 3 Hz, 1 H, C*H*OH),

5.10 (d, J = 10 Hz, 1 H, terminal =CH), 5.19 (d, J = 16 Hz, 1 H, terminal =CH), 5.45 (q, 1 H, =C*H*CH_2), 6.05 (t, 1 H, CH_2=CH-C*H*=), 6.66 (dt, J = 15, 9 Hz, 1 H, CH_2=C*H*); NMR (C_6D_6) δ 1.0–1.8 (m, 18 H), 1.97 (eight line m, 1 H, C*H*CH_2OH), 2.23 (m, 1 H, =CCH), 2.27 (m, 1 H, C(3a)H), 2.37 (m, 1 H, =CCH), 3.00 (broad s, 1 H, C(1)H), 3.34 (dt, J = 11, 5 Hz, 1 H, C(9a)H), 3.68 (dt, J = 10, 4 Hz, 1 H, C*H*OH), 4.00 (td, J = 10, 3 Hz, 1 H, C*H*OH), 5.07 (d, J = 10 Hz, 1 H, terminal =CH), 5.17 (d, J = 16 Hz, 1 H, terminal =CH), 5.39 (q, J = 7 Hz, 1 H, =C*H*CH_2), 6.10 (t, J = 9 Hz, 1 H, CH_2=CHC*H*=), 6.68 (dt, J = 15, 9 Hz, 1 H, CH_2=C*H*); exact mass calcd for $C_{19}H_{31}NO$ m/e 289.2405, found m/e 289.2414.

Acknowledgment. We thank Richard Weisenberger and Dr. Charles Cottrell for their assistance in obtaining mass and 300-MHz ^{1}H NMR spectra, respectively, at The Ohio State University Chemical Instrument Center. Financial support from The National Institutes of Health (GM-27647) is gratefully acknowledged. We also thank the NIH for a grant (GM-27431) to Ohio State University in support of the acquisition of a Bruker WM 200-MHz NMR spectrometer used during the course of this research. We thank Yeun-Min Tsai for performing the free radical chemistry presented herein.

Registry No. (±)-**1**, 75685-48-2; (±)-**2**, 84275-40-1; (±)-**5**, 78341-47-6; (±)-**6**, 78341-48-7; (±)-**7**, 78341-49-8; (±)-**8**, 78308-01-7; (±)-**9**, 78308-02-8; (±)-**10**, 78308-03-9; (±)-**11** (isomer 1), 84236-36-2; (±)-**11** (isomer 2), 84236-39-5; (±)-**13**, 78308-05-1; (±)-**14**, 78308-06-2; (±)-**16**, 78308-08-4; (±)-**17** (isomer 1), 84236-37-3; (±)-**17** (isomer 2), 84236-38-4; (±)-**18**, 80664-54-6; (±)-**19**, 78308-09-5; (±)-**20**, 78308-10-8; (±)-**21**, 78308-11-9; (±)-**22**, 78392-00-4; (±)-**23**, 78308-12-0; (±)-**24**, 78341-51-2; (±)-**25**, 78328-74-2; (±)-**26**, 78392-01-5; (±)-**27**, 75685-52-8; (±)-**28**, 78392-02-6; (±)-**29**, 84175-95-1; (±)-**30**, 84175-96-2; (±)-**31**, 84236-40-8; (±)-**32**, 84175-97-3; (±)-**33**, 84175-98-4; (±)-**34**, 84236-41-9; (±)-**35**, 84175-99-5; (±)-**36**, 84176-00-1; (±)-**37**, 84176-01-2; (±)-**38**, 84176-02-3; (±)-**39**, 84176-03-4; (±)-**40**, 84236-42-0; (±)-**41**, 84236-43-1; 2-cyclohexen-1-one, 930-68-7; 1,3-butadiene, 106-99-0; succinimide, 123-56-8; ethyl bromoacetate, 105-36-2; *tert*-butylchlorodiphenylsilane, 58479-61-1; pinacol (*E*)-1-(trimethylsilyl)-1-propene-3-boronate, 79309-68-5; 1-(trimethylsilyl)-3-*tert*-butyldimethylsilyl-1-propyne, 78978-51-5.

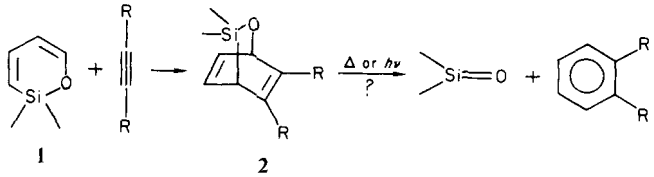
Direct Thermal and Photochemical Generation of Silanones[1]

Gregory Hussmann, William D. Wulff, and Thomas J. Barton*

Contribution from the Department of Chemistry, Iowa State University, Ames, Iowa 50011.
Received August 9, 1982

Abstract: 2-Silapyrans (1,2-oxasilins) are synthesized by the pyrolysis of 1-disilanyl-4-methoxy-1,3-butadienes via initial 1,5-silyl migration to afford an intermediate 1-sila-1,3-butadiene. Diels–Alder reaction of the silapyrans and perfluoro-2-butyne does not lead to isolable adducts but rather leads to apparent extrusion of silanone (R_2Si=O), which is trapped by a variety of reagents. Reaction of the silapyrans and maleic anhydride provides stable adducts that extrude silanones upon either thermolysis or photolysis. No evidence could be found for rearrangement of a silylsilanone to a siloxysilylene.

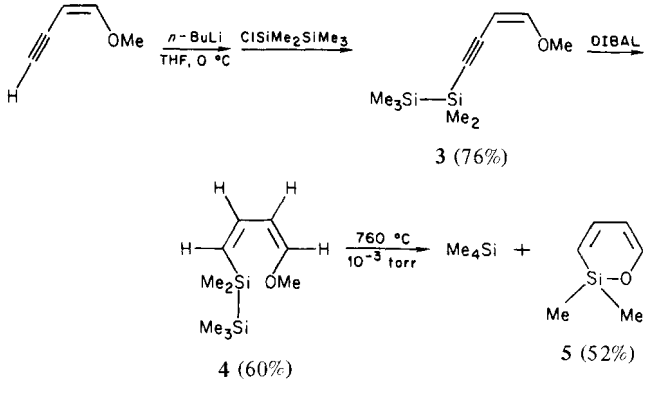
Silanones,[2] compounds containing a silicon–oxygen double bond, have been suggested as transient intermediates in a variety of reactions since 1952 when Andrianov and Sokolov proposed their involvement in the thermal redistribution of polydimethylsiloxanes.[3] However, the study of these intriguing ketone analogues has been hampered by the lack of a convenient precursor. From the onset the ultimate goal of this project was the synthesis of a convenient thermal and/or photochemical silanone precursor from which the generation of silanone would not be accompanied by the production of products reactive to silanones. Thus, we selected the 7-oxa-8-silabicyclo[2.2.2]octadiene (**2**) ring system as our target. This



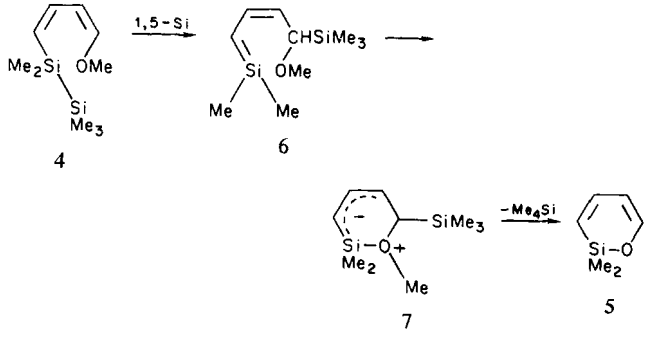
1 2

choice was predicated by the knowledge that silenes[4] and disilenes[5] had been successfully generated by thermally induced retrograde Diels–Alder reactions of the 7-sila- and 7,8-disilabicyclo[2.2.2]-octadienes. The obvious route to **2** would be a Diels–Alder reaction between a 1,2-oxasilin (**1**) and an acetylene. However, no good synthetic route to the 1,2-oxasilin ring existed.

Scheme I



Scheme II



Results and Discussion

This research had as its origin the serendipitous discovery that flash vacuum pyrolysis (FVP) of (*Z*,*Z*)-1-(pentamethyldi-

(1) A preliminary account of a portion of this work has appeared: Barton, T. J.; Wulff, W. D. *J. Am. Chem. Soc.* **1979**, *101*, 2735.
(2) For a general review of π-bonded silicon see: Gusel'nikov, L. E.; Nametkin, N. S. *Chem. Rev.* **1979**, *79*, 529.
(3) Andrianov, K. A.; Sokolov, N. N. *Dokl. Akad. Nauk SSSR* **1952**, *82*, 909.
(4) Barton, T. J.; Kline, E. A. *J. Organomet. Chem.* **1972**, *42*, C21.
(5) Roark, D. N.; Peddle, G. J. D. *J. Am. Chem. Soc.* **1972**, *94*, 5837.

0002-7863/83/1505-1263$01.50/0