Importance of Allylic Interactions and Stereoelectronic Effects in Dictating the Steric Course of the Reaction of Iminium Ions with Nucleophiles. An Efficient Total Synthesis of (±)-Gephyrotoxin[1]

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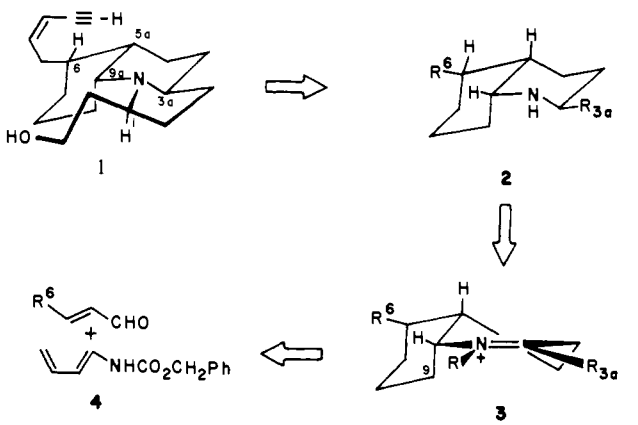
Abstract: A stereocontrolled total synthesis of (±)-gephyrotoxin in 15 steps and 6.5% overall yield from benzyl *trans*-1,3-butadiene-1-carbamate is described. A key step is reduction of octahydroquinoline **27** from the more hindered concave α face to provide decahydroquinoline **28**. This unusual transformation results from the interplay of allylic ($A^{1,2}$) steric interactions and stereoelectronic effects.

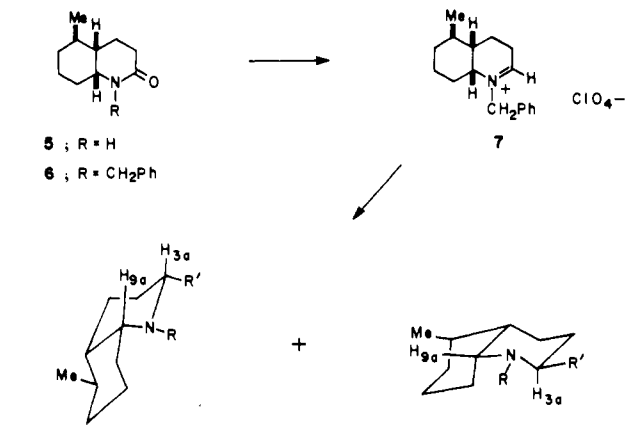
Gephyrotoxin (**1**), the parent member of a new class of skin alkaloids from tropical poison frogs of the genus *Dendrobates*,[2] was first described by Daly, Witkop, and co-workers in 1977.[3] Mild muscarinic activity was originally reported for this alkaloid,[4] while more recent studies[5] have revealed a more complex and interesting array of neurological activities associated with gephyrotoxin. The unusual chemical and biological characteristics of gephyrotoxin have stimulated synthetic activity in numerous laboratories.[2,6-9] In conjunction with our own interest in the biological activity[5,10] of this series, we have been exploring simplified approaches to gephyrotoxin and gephyrotoxin analogs that might be appropriate for preparing reasonable quantities of these materials.

In this paper we detail a concise approach to (±)-gephyrotoxin (**1**) that yields (±)-**1** in 15 steps and 6.5% overall yield from readily available[11] benzyl *trans*-1,3-butadiene-1-carbamate (**4**). New insights into the delicate interplay of stereoelectronic[12] and allylic conformational effects[13] in controlling the steric course of the reaction of cyclic iminium ions with nucleophiles are also recorded.

Scheme I



Scheme II



Results and Discussion

Our general strategy is outlined in Scheme I. The key step is reduction of bicyclic iminium ion **3** (R = electrophilic metal species) *from the sterically more congested concave α-face.* The rationale for this unusual transformation[14] is that iminium ions

(1) Paper 14 in the series Synthetic Applications of *N*-Acylamino-1,3-dienes. For part 13, see ref 8b.

(2) For a recent review of these fascinating natural products, see: Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205–340.

(3) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128–1140. Daly, J. W.; Brown, G. B.; Mensah-Dwunah, M.; Myers, C W. *Toxicon*, **1978**, *16*, 163–188.

(4) Mensah-Dwumah, M.; Daly, J. W. *Toxicon* **1978**, *16*, 189–194.

(5) Souccar, C.; Maleque, M. A.; Daly, J. W.; Albuquerque, E. X. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1982**, *41*, 1299.

(6) For a total synthesis of (+)-gephyrotoxin, see: Fujimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981**, *42*, 4197–4198. There is current disagreement[2] on the absolute configuration of the natural alkaloid.

(7) For previous total synthesis of (±)-gephyrotoxin, see: Fujimoto, R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7154–7156. Hart, D. J.; Kanai, K.-I. *Ibid.* **1983**, *105*, 1255–1263. For a formal total synthesis, see: Hart, D. J. *J. Org. Chem.* **1981**, *46*, 3576–3578.

(8) For previous total syntheses of (±)-perhydrogephyrotoxin, see: (a) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454–1456. (b) Overman, L. E.; Freerks, R. F. *J. Org. Chem.* **1981**, *46*, 2833–2835.

(9) For syntheses of the racemic perhydropyrrolo[1,2-*a*]quinoline ring system, see: Habermehl, G. G.; Thurau, O. *Naturwissenschaften* **1980**, *67*, 193. Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367–373.

(10) Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Eldefrawri, M. E.; Nimit, Y.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *22*, 565–573.

(11) Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Org. Synth.* **1979**, *59*, 1–9.

(12) The importance of maintaining maximum orbital overlap with respect to the incoming nucleophile and the developing lone-electron pair on nitrogen in nucleophilic additions to six-membered ring iminium ions has been stressed by several investigators, see, inter alia: Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032–7035, *J. Chem. Soc., Chem. Commun.* **1982**, 102–103. Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054–1068. Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *Ibid.* **1976**, *98*, 3645–3655. Ziegler, F. E.; Spitzner, E. B. *Ibid.* **1973**, *95*, 7146–7149 and ref 8a,b.

(13) For a review, see: Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.

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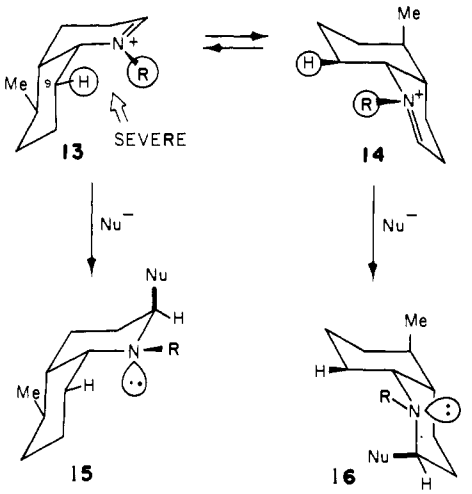
Scheme III



of this type should be preferentially reduced *via* transition-state conformers related to **3**, since the alternate conformer would be destabilized by $A^{1,2}$ interactions[13] between R and C_9.[15] A stereoelectronic preference[12] for initial trans diaxial alignment of an entering hydride nucleophile and the developing lone-electron pair on nitrogen would then lead to decahydroquinoline **2**. The dienamide Diels–Alder approach we had previously developed for the total synthesis of (±)-pumiliotoxin C[16] was envisaged to provide ready access to bicyclic intermediate **3**.

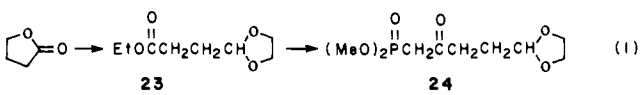
Model Studies. Allylic Interactions and Stereoelectronic Effects in the Reaction of *cis*-Octahydroquinolinium Ions with Nucleophiles. The synthesis plan we have just outlined had its origin in the following model study. In our earliest approach to gephyrotoxin, we explored the reaction of organometallic nucleophiles and model octahydroquinolinium ion **7**, under the (mistaken) assumption that the elements of the gephyrotoxin C ring could be added by convex addition of an organometallic nucleophile to iminium ions of this type.[17] Iminium ion **7** was prepared from the known lactam **5**[16] by N-benzylation, followed by carefully controlled reduction with diisobutylaluminum hydride and acidification at low temperature with ethanolic perchloric acid.[18] The reaction of **7** with either *n*-BuLi or *n*-$C_5H_{11}MgBr$ (−78 °C, THF) gave only traces of the desired addition products and led primarily to reduction product **8** (Scheme II). The structure of **8** was confirmed by its preparation from **6** by reaction with $LiAlH_4$. In contrast, the reaction of 1-pentynyl lithium with **7** proceeded in modest efficiency under similar conditions to give adduct **9** as the major product. Separation by thin layer chromatography provided pure **9** in 30% yield and stereoisomer **10** in 5% yield. That the major product had indeed arisen by organometallic addition from the more hindered concave α face was confirmed by catalytic hydrogenation of **9** to give *cis*-decahydroquinoline salt **11** (mp 193–195 °C), which we had previously prepared[19] by the unambiguous sequence[16] used to synthesize (±)-pumiliotoxin C. Decahydroquinoline salt **11** showed a diagnostic[16] narrow multiplet (half-height width = 8 Hz) for angular hydrogen H_{9a}[15] and ^{13}C NMR[20] signals for the ring carbons (e.g., C_{3a} 60.3, C_{9a} 58.1 ppm)[15] that were essentially identical[16] with those of pumiliotoxin C hydrochloride. Similarly, **10** was characterized by conversion to **12**. *cis*-Decahydroquinoline **12** showed characteristic broad multiplets in the ^1H NMR spectrum between δ 2.4–3.6 for H_{9a} and H_{3a} and diagnostic[8b,20] ^{13}C NMR signals at 51.6 and 51.4 ppm for C_{3a} and C_{9a}.[15] The upfield position[20] of these signals rules out a trans ring fusion for **12** (and **10**) and, thus, confirms that **12** and **11** differ only in configuration at C_{3a}.

That nucleophilic addition to **7** should occur preferentially from the obviously more hindered concave α face may be rationalized as illustrated in Scheme III. Stereoelectronically controlled[12] addition to iminium ion **7** can occur via two transition states, related to the *cis*-octahydroquinolinium ion conformers **13** and **14**, to give **15** and **16**,[21] respectively. The $A^{1,2}$ interaction[13] between R and C_9 is apparently sufficiently severe in the transition state related to conformer **13** that addition occurs in the alternate sense, in spite of the 1,3-diaxial interaction that is developing[21] between C_9 and the nucleophile in this (**14** → **16**) process. That addition occurs preferentially from the concave face, in spite of this 1,3-diaxial interaction, likely reflects the small size of an alkynyl lithium nucleophile[22] and the early transition state[24] of the exothermic reaction of an iminium ion with an alkynyl anion.

Clearly, the logic of the analysis advanced in Scheme III suggests the synthetic approach to gephyrotoxin, which was outlined in Scheme I. That an imine such as **3** could be reduced from the more hindered concave α face was first[14] demonstrated by us within the context of a (±)-perhydrogephyrotoxin synthesis.[8b] The application of this strategy to prepare (±)-gephyrotoxin is detailed in the following section.

Total Synthesis of (±)-Gephyrotoxin. The initial Diels–Alder stage is summarized in Scheme IV. Dienophile **20** was easily obtained (30% overall yield) from 3-butynol (**17**) by the standard sequence outlined in Scheme IV. Cycloaddition of **20** with excess benzyl *trans*-1,3-butadiene-1-carbamate (**4**) was cleanly accomplished at 110 °C (1.5 h) to provide a 9:1 mixture[25] of endo (**21**) and exo (**22**) cycloadducts. Excess diene **4** was recovered (80% efficiency) by chromatography on silica gel, and the mixture of cycloadducts was isolated in crystalline form in 81% yield. The use of excess diene in the cycloaddition step was critical. The shorter reaction times occasioned by this modification completely suppressed the epimerization of the *endo* adduct at C_{5a},[15] which had previously plagued similar cycloadditions.[16,8] Nearly pure samples of the endo adduct **21** (mp 46 °C) and the exo adduct **22** (mp 91 °C) could be obtained by a combination of chromatography and crystallization, although isomer separation was very inefficient at this stage. Our previous experience with related cycloadditions[16,8] allowed stereochemical assignments to be confidently made on the basis of NMR spectra (see Experimental Section).

Reaction of the cycloadduct mixture with the sodium salt of readily available[26] ketophosphonate **24** (eq 1) was seriously



(1)

(14) The importance of allylic and stereoelectronic effects in dictating the course of nucleophilic addition to iminium ions of this type was first pointed out by us in 1980[8a] and applied specifically to reductions in 1981.[8b] A related rationale has been advanced recently for stereocontrol of somewhat similar reductions of tetrahydropyridines, see: Matsumura, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1982**, *23*, 1929–1932.

(15) The numbering used for all intermediates corresponds to that of gephyrotoxin; see ref 3 and structure **1**.

(16) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179–5185.

(17) A modification of this strategy, which culminated in the first synthesis of perhydrogephyrotoxin, is described in ref 8a.

(18) For related conversions of lactams to iminium ions (or the related enamines), see: Bohlmann, F.; Müller, H.-J.; Schumann, D. *Chem. Ber.* **1973**, *106*, 3026–3034. Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1969**, 877–878. Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064–5074.

(19) Unpublished studies of Dr. Peter Jessup. The approach was identical with that described in ref 16.

(20) The ^{13}C NMR of decahydroquinolines has been well defined, see: Booth, H.; Griffiths, D. V.; Jozefowicz, M. L. *J. Chem. Soc., Perkin Trans. 2.* **1976**, 751–760. Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1977**, *42*, 51–62; **1976**, *41*, 199–208.

(21) At what point along the reaction coordinate **16** undergoes conformational interconversion to the more stable *cis*-decahydroquinoline conformer with Nu and Me equatorial (cf. structure **9**) is, to our knowledge, completely unknown.

(22) The degree of association of 1-pentynyllithium in THF is not, to our knowledge, known.[23]

(23) Cf.: Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon: Oxford, 1974; Chapter 1.

(24) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

(25) A 20-cm DuPont Zorbax PSM-60 column and a 1:4 ethyl acetate/hexane eluent were used for this analysis.

(26) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5653–5655.

Scheme IV

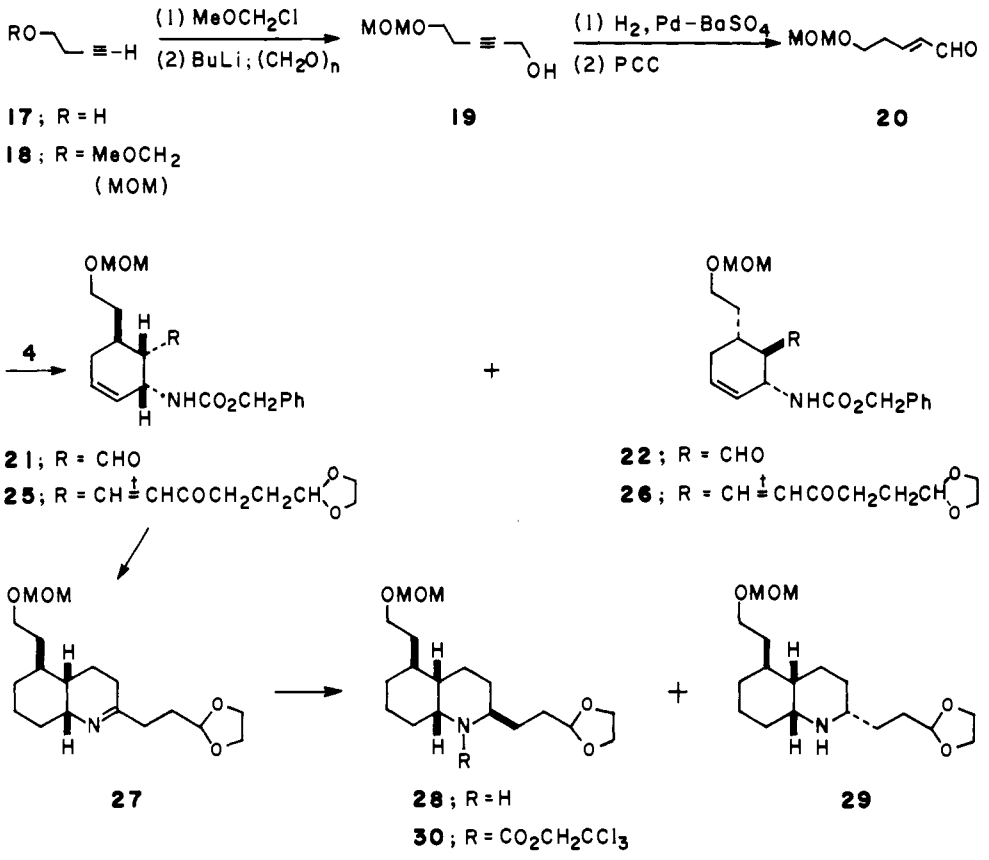


Table I. Reduction of *cis*-Octahydroquinolines under Various Conditions

	imine		reduction conditions			stereoisomer ratio
entry	R^1	R^2	reducing[a] agent	solvent	temp, °C	
1	OMOM	$CHOCH_2CH_2O$ 27	$LiAlH_4$	Et_2O	−35[c]	no reaction
2			$LiAlH_4$	Et_2O	−10[b]	5:1
3			$LiAlH_4$	Et_2O	−19[c]	9:1 to 16:1[d]
4			i-$Bu_3Al/LiAlH_4$[g]	THF	−78 to 0[f]	2-5:1
5			$Me_3Al/LiAlH_4$[g]	THF	−78 to 10[f]	1:1[e]
6	n-C_3H_7	$CH_2CH_2CHOCH_2CH_2O$	$NaBH_4$	MeOH	25	4:96
7			H_2/Pd–C	EtOAc	25	2:98
8	n-C_3H_7	$CH_2CH_2CH_2OMe$	$LiAlH_4$	Et_2O	−15[f]	6:1
9			$LiAlH_4/AlH_3$[g]	Et_2O	−15[f]	1:1
10			$LiAlH_4/LiClO_4$[h]	Et_2O	−15[f]	8:1
11			$LiAlH_4/BEt_3$[g]	Et_2O	−15[f]	8:1
12			$LiAlH_4/AlEt_3$[g]	Et_2O	−15[f]	8:1
13			$NaEt_3BH$	Et_2O	−10[f]	5:95

[a] Unless noted otherwise a large excess (5–25 equiv) of the reducing agent was employed. Stereoisomer ratios were determined from careful integration of the 250-MHz ^1H NMR spectrum of crude reduction products. [b] Estimated internal temperature. Bath temperature was −17 °C. [c] Internal temperature. [d] Range of three experiments. [e] Isomer ratio was similar when 27 was treated first with Me_3Al at −78 °C and then $LiAlH_4$ was added at that temperature. [f] External bath temperature. [g] Molar ratio 1:1. [h] Molar ratio 4:1.

compromised by competing epimerization of aldehyde **21**. However, use of the more soluble lithium salt of **24** allowed the reaction to be completed within 5 h at −70 °C, conditions that completely suppressed epimerization of **21**. Chromatography on silica gel easily separated the stereoisomeric adducts to provide **25** as a pure colorless oil in 89% yield. Enone **26** derived from the contaminating amounts of exo cycloadduct **22**, was isolated as a crystalline solid (mp 89 °C) in ~4% yield.

A critical stage in our synthesis plan was the projected conversion of **25** to bicyclic imine **27**. This conversion would have to be accomplished under carefully controlled conditions, since catalytic hydrogenation of **27** would assuredly occur[16] from the undesired convex face. To accomplish the desired transformation, **25** was hydrogenated in the presence of a large excess of CF_3CO_2H until 2 equiv of H_2 had been consumed. Under these strongly acid conditions the resulting keto ammonium salt does not cyclize to the conjugate acid of **27**.[8b] Removal of excess H_2 and partitioning of the keto ammonium salt between 1 N NaOH and $CHCl_3$ cleanly provided the desired *cis*-octahydroquinoline **27** in 94% yield. Imine **27** showed diagnostic signals for the C=N grouping at 1658 cm^{-1} in the infrared spectrum and 170.6 ppm in the ^{13}C NMR spectrum.

The reduction of imine **27**, and other closely related imines prepared earlier in our laboratory,[27] with a variety of reductants

is summarized in Table I. Although the data are not completely logically persuasive, several trends are in accord with the analysis advanced in Scheme III. Thus, bulky (entries 7 and 13) or weak (entry 6) reducing agents react with high selectivity from the less hindered convex face. The inability of added Lewis acids (entries 4, 5, 11, and 12) to enhance the desired selectivity that was obtained with $LiAlH_4$ is surprising in light of the observations of Yamamoto.[14] Nonetheless, a good level of stereocontrol could be obtained with $LiAlH_4$, if the reaction temperature was *carefully* controlled (see entries 1–3).

Reduction of imine **27** under optimum conditions (ether at −19 °C with excess powdered $LiAlH_4$) proceeded in quantitative yield to give *cis*-decahydroquinolines **28** and **29** in a ratio of ~12:1. The stereostructure of the major product **28** followed directly from its ^1H NMR spectra, which showed H_{9a}[15] as a doublet of triplets (J = 11.8, 4.2 Hz) at δ 3.08 and H_{3a}[15] as a broad multiplet at δ 2.7–2.85. The secondary amine grouping of **28** was surprisingly unreactive, and acylation of the crude reduction product with 2,2,2-trichloroethyl chloroformate[28] was best accomplished in the presence of 1,2,2,6,6-pentamethylpiperidine.[29] Purification on silica gel provided key intermediate **30** in 85% yield as an isomerically pure colorless oil.

The gephyrotoxin C ring and C_1 side chain were readily elaborated by an intramolecular Michael approach (Scheme V). Thus, **30** was treated at room temperature with a 1:1 mixture of 10% $HClO_4$ and THF to effect selective cleavage of the acetal, and the resulting aldehyde was immediately condensed with (formylmethylene)triphenylphosphorane[30] to give **31** in 75% yield.[31] Enal **31** was converted to the key tricyclic intermediate **34** by a three-step sequence. Treatment of **31** with MeOH in the presence of pyridinium *p*-toluenesulfonate[32] provided **32**, from which the (trichloroethoxy)carbonyl protecting group was best removed[33,34] by basic hydrolysis to afford crude **33** in 96% yield from **31**. Amine acetal **33** was not purified but immediately dissolved in THF and converted to tricycle **34** by sequential one-pot treatment at room temperature with (i) 1 N HCl, (ii) NaOMe, and (iii) $NaBH_4$. Purification on alumina provided pure **34** in 56% yield. Also isolated was 8% of the primary acetate, apparently formed[34] from **34** and ethyl acetate during chromatographic purification on alumina. No trace of a tricyclic isomer of **34** was seen from a careful examination of chromatographic fractions. Clearly, the intramolecular Michael ring closure of the amine enal formed from **33** is highly stereoselective, more so than cyclization[8a] of a closely related amine vinyl ester. Whether the high selectivity in the present case derives from kinetic or thermodynamic control is unknown.

Perhydropyrroloquinoline **34** showed diagnostic signals for the CH_2O hydrogens of the intramolecularly hydrogen-bonded 2-hydroxyethyl substituent at δ 4.01 (dt, J = 11.3, 2.4 Hz) and 3.64 (dt, J = 11.1, 3.6 Hz). Nearly identical signals are seen for this methylene group in gephyrotoxin.[1] Conversion[35,36] to *tert*-butyldiphenylsilyl ether **35** was readily accomplished (83% yield), and the hydrochloride salt of this intermediate melted sharply at 144–145 °C.

The synthesis of gephyrotoxin was completed by the method of Corey and Rücker[38] to introduce the *cis*-enyne grouping. Treatment of **35** with 2 equiv of 24% HBr in 1,2-dimethoxyethane at 50 °C selectively removed the methoxymethyl protecting group to deliver **36** in 86% yield. Oxidation of **36** with the Swern reagent[37] provided **37**. Reaction of aldehyde **37** with the lithium salt of 1,3-bis(triisopropylsilyl)propyne[38] at −78 °C → room temperature gave a 9:1 mixture of **38** and the corresponding trans stereoisomer in 55% overall yield from **37**. Cleavage of both silyl groups (n-Bu_4NF, DMF) followed by careful purification on silica gel gave isomerically pure (±)-gephyrotoxin (**1**) in 58% yield. A second fraction (41%), which was a 3:1 mixture of **1** and its trans stereoisomer, was also isolated. Synthetic (±)-gephyrotoxin was identical [250-MHz ^1H NMR, TLC on alumina and silica gel] with an authentic sample kindly provided by Professor Hart.[7]

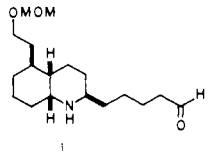
Conclusion

The total synthesis of (±)-gephyrotoxin has been accomplished in 15 steps and 6.5% overall yield from readily available[11] acylamino-1,3-diene **4**. An excellent level of stereocontrol was obtained at each stage: Diels–Alder reaction (9:1), reduction (12:1), cyclization (>15:1). Of equal importance, this synthesis exercise provides added insight into the role of stereoelectronic effects and allylic conformation interactions in controlling the steric course of the reaction of cyclic iminium ions with nucleophiles.

Experimental Section[39]

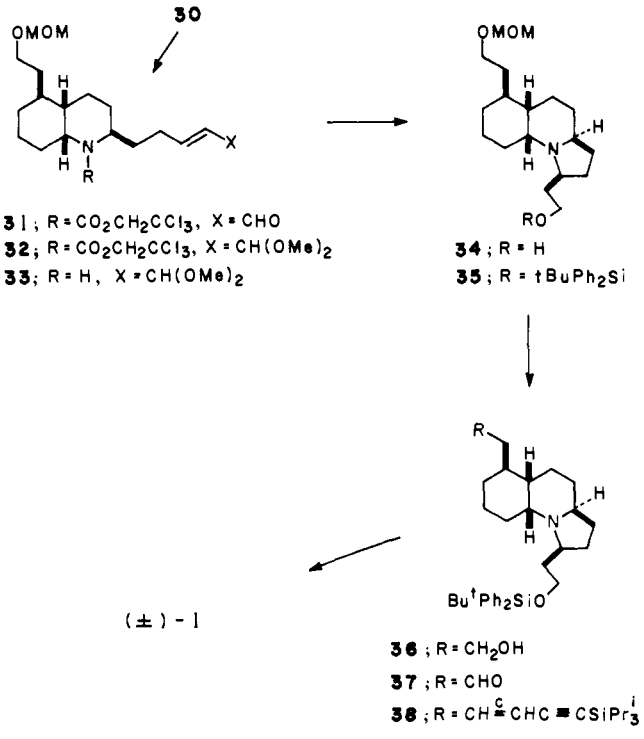
(4aα,5α,8aα)-1-Benzyl-5-methyl-3,4,4a,5,6,7,8,8a-octahydroquinolinium perchlorate (7). To a solution of lactam **6** [500 mg, 1.95 mmol; prepared from **5**[16] in 94% yield by reaction with NaH (1.3 equiv) and benzyl bromide (2.2 equiv) in THF at 40 °C] and dry ether (6 mL) was added diisobutylaluminum hydride (1.95 mL of a 1 M solution in hexane) by drops at −78 °C. After an additional 1.5 h at −78 °C, a 10% solution of $HClO_4$ in ethanol was added dropwise at −78 °C to the rapidly stirred reaction mixture until the pH of an aliquot was ~1 (after dilution with a little H_2O). The resulting mixture was stirred for an additional 1 h at −78 °C, and the ethereal layer was decanted (~20% of **6** is recovered from this layer). The residue was washed with 1:1 ether/

(27) These experiments were conducted by R. Freerks.
(28) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555–2558.
(29) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5444–5450.
(30) Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 2130–2133.
(31) Our initial attempts to prepare **31** by the approach utilized in our (±)-perhydrogephyrotoxin[8b] synthesis, in which the entire elements of the B and C rings are added in the olefination step, were unsatisfactory. The problem arose with the conversion of i → **31**. The conditions we had employed previously[8b] proved incompatible with the methoxymethyl ether grouping. Other methods for dehydrogenation (e.g., selenation–oxidation) also proceeded with unacceptable efficiencies.



(32) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.
(33) (a) Deprotection under reductive conditions[8b,33b] was markedly inferior. (b) Cf.: Just, G.; Grozinger, K. *Synthesis* **1976**, 457–458.
(34) Cf: Posner, G. H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487–496.
(35) Hanessian, S.; Lavalle, P. *Can. J. Chem.* **1975**, *53*, 2975–2977.
(36) Chaudhary, S. K.; Hernanadez, O. *Tetrahedron Lett.* **1979**, 99–102.
(37) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
(38) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, 719–722.
(39) In cases where synthetic intermediates or products were isolated by "aqueous workup (organic solvent, drying agent)", the procedure was to quench the reaction mixture with H_2O, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic layers with the indicated drying agent, and remove the solvent with a rotary evaporator at reduced pressure. When "basic workup (organic solvent, drying agent)" is indicated, the procedure was similar except the indicated basic quenching solution was used instead of H_2O. Tetrahydrofuran (THF) and ether were distilled from sodium and benzophenone. Dimethylformamide (DMF) was distilled from CaH_2 at 20 mm. Benzene, CH_2Cl_2, i-Pr_2NEt, and pyridine were distilled from CaH_2. The molarities indicated for butyllithium were established by titration with 2,5-dimethoxybenzyl alcohol.[40] ^1H NMR and ^{13}C NMR spectra were determined at 250 MHz and 63 MHz, respectively, with a Bruker WM 250 spectrometer, or ^1H NMR were determined at 80 MHz with a Varian FT-80 spectrometer. ^1H NMR and ^{13}C NMR shifts are reported as δ values in parts per million relative to internal tetramethylsilane. ^1H NMR coupling constants (J) are reported in hertz, and they refer to apparent multiplicities and not true coupling constants; abbreviations used are as follows: s, singlet; d, doublet; t, triplet, and m, complex multiplet. These same abbreviations are used to denote the multiplicities in off-resonance ^{13}C NMR spectra. Infrared spectra were determined with a Perkin-Elmer Model 283 spectrometer. Electron-impact and high-resolution mass spectra were determined with a Kratos MS-50 spectrometer at the Midwest Center for Mass Spectroscopy, University of Nebraska. Chemical-ionization mass spectra were determined on a Finnigan 4000 GC/MS/DS with isobutane as the reagent gas. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. TLC and column chromatography utilized E. Merck silica gel. Capillary GC analyses were done with a Hewlett-Packard Model 5880 gas chromatograph with flame ionization detection. High-performance LC (HPLC) analyses were obtained with Waters components, including a 6000A pump, U5K injector, and R401 differential refractometer. All reactions were run under a nitrogen or argon atmosphere.
(40) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87–88.

Scheme V



hexane (3×) and the residual oil was dried in vacuo to give ~470 mg (70%) of crude **7** as a colorless foam, which resisted all attempts at crystallization: ^{1}H NMR (60 MHz, $CDCl_3$) 1.00 (d, J = 6 Hz, Me), 5.02 (apparent s, CH_2Ph), 7.2–7.8 (m, Ph), 8.68 (m, half-height width = 8 Hz, N=CH). Iminium ion samples of this purity were used directly in subsequent reactions.

Reaction of Iminium Ion 7 with 1-Pentynyllithium. A solution of the iminium ion sample described in the previous experiment and dry THF (10 mL) was added dropwise to ~10 equiv of 1-pentynyl lithium (~0.2 M in THF/hexane, from 1-pentyne and *n*-BuLi) at −78 °C. The resulting solution was maintained at −78 °C for 2 h and left at −20 °C overnight. The reaction was quenched at room temperature by adding 1 mL of saturated aqueous NH_4Cl solution, and the resulting mixture was concentrated. This residue was extracted with ethyl acetate (3 × 50 mL), and the extract was dried (K_2CO_3). Concentration, followed by purification of the residue by preparative TLC (silica gel, 9:1 hexane/ethyl acetate) gave in the highest R_f band 20 mg (5%) of **10** as a colorless oil: ^{1}H NMR (60 MHz, $CDCl_3$) 7.0–7.6 (m, Ph), 3.57 (AB q, J = 15 Hz, $\Delta\nu$ = 46 Hz, CH_2Ph), 3.3–3.6 (m, 1 H), 2.7–3.0 (m, 1 H); ^{13}C NMR (23 MHz, $CDCl_3$) 140.7, 129.0, 128.2, 126.6, 86.1, 55.2, 53.4, 50.0, 44.5, 36.0, 29.9, 28.3, 26.7, 23.4, 22.9, 20.9, 20.8, 19.8, 13.6. Adduct **10** was characterized by treatment with H_2 (1 atm, Pd/C, EtOH, 25 °C) and crystallization of the hydrochloride salt from ether/hexane to give **12**: mp 180–181 °C; ^{1}H NMR (60 MHz, $CDCl_3$) 9–10 (br m, NH_2), 2.4–3.6 (br m, H_{3a} and H_{9a});[15] ^{13}C NMR (23 MHz, $CDCl_3$)[15] 51.6 (C_{3a} or C_{9a}), 51.4 (C_{3a} or C_{9a}), 38.6 (C_{5a}), 32.0, 31.9, 31.5, 29.7, 27.9, 25.5, 24.1, 23.2, 22.5, 19.7, 18.9, 13.6; MS (EI), m/e (relative intensity) 223 (M, 3), 152 (100).

A lower R_f band gave 130 mg (30%) of **9** as a colorless oil: ^{1}H NMR (60 MHz, $CDCl_3$) 7.0–7.6 (m, Ph), 3.91 (s, CH_2Ph), 3.0–3.3 (m, 1 H), 2.5–2.7 (m, 1 H); ^{13}C NMR (23 MHz, $CDCl_3$) 140.0, 129.1, 127.9, 126.5, 84.2, 82.7, 58.8, 56.2, 50.1, 43.9, 32.1, 31.2 (2C), 26.1, 24.5, 22.5, 21.0, 20.9, 19.5, 13.5. Adduct **9** was characterized by treatment with H_2 (1 atm, Pd/C, EtOH, 25 °C) and crystallization of the hydrochloride salt from ether/hexane to give **11**: mp 193–195 °C; IR (Nujol) 2500–3000, 1575 cm^{-1}, ^{1}H NMR (60 MHz, $CDCl_3$)[15] 5–6 (br, m, NH_2), 2.8–3.1 (narrow m, half-height width = 8 Hz, H_{9a}), 2.4–2.8 (m, H_{3a}); ^{13}C NMR (23 MHz, $CDCl_3$)[15] 60.3 (C_{3a}), 58.1 (C_{9a}), 41.0 (C_{5a}), 35.0 (C_7), 32.5, 31.5, 29.2 (C_9), 27.3 (C_6), 25.7, 25.3 (C_4), 22.8, 20.7 (C_8), 19.8 (Me), 14.0 (Me); MS (EI), m/e (relative intensity) 223 (M, 2), 180 (13), 153 (11), 152 (100). Anal. Calcd for $C_{15}H_{30}ClN$: C, 69.34; H, 11.64; N, 5.39. Found: C, 69.07; H, 11.37; N, 5.49. This sample was identical (mp, ^{1}H NMR, ^{13}C NMR) with a sample prepared[19] by the unambiguous sequence of ref 16.

5-(Methoxymethoxy)-2-pentyn-1-ol (19). A solution of 2-pentyn-1-ol (**17**, 11.6 g, 0.166 mol), *i*-Pr_2NEt (28.8 mL, 0.166 mol), and CH_2Cl_2 was cooled to 0 °C, and a solution of $ClCH_2OMe$ (**CAUTION**: cancer suspect chemical; 9.6 mL, 0.166 mol) and CH_2Cl_2 (150 mL) was added by drops over 30 min. Aqueous workup (CH_2Cl_2, $MgSO_4$) followed by trap-to-trap distillation (room temperature, 0.2 mm) gave 17 g (90%) of nearly pure **18** as a colorless liquid: ^{1}H NMR (60 MHz, $CDCl_3$) 2.0 (t, J = 2 Hz, ≡CH), 2.5 (dt, J = 2,7 Hz, CH_2C≡), 3.4 (s, OMe), 3.65 (t, J = 7 Hz, CH_2O), 4.6 (s, OCH_2O). Distillation (bp 135–140 °C) resulted in significant decomposition, however, material purified by trap-to-trap distillation was satisfactory for the next step.

A solution of **18** (18.8 g, 0.165 mol) and THF (200 mL) was treated dropwise at −78 °C with BuLi (127 mL of a 1.3 M solution in hexane, 0.165 mol), and the resulting solution was allowed to warm to room temperature overnight. Paraformaldehyde (6 g, 0.2 mol; finely powdered and dried in vacuo for 24 h) was added followed by THF (200 mL). The resulting mixture was heated at reflux for 2 h, and after cooling to room temperature, was poured into saturated aqueous NH_4Cl (100 mL). The organic layer was washed with saturated aqueous NH_4Cl (2 × 40 mL), dried ($MgSO_4$), and concentrated. Distillation gave an initial fraction (1.2 g, 6.4%, bp 40–50 °C, 11 mm) of **18**, followed by 13.3 g (56%) of pure alcohol **19** as a colorless liquid: bp 96 °C (1.1 mm); ^{1}H NMR (80 MHz, $CDCl_3$) 2.23 (br s, OH), 2.52 (tt, J = 6.8, 2.1 Hz, ≡CCH_2), 3.38 (s, OMe), 3.65 (t, J = 6.8 Hz, ≡CCH_2CH_2), 4.24 (br s, CH_2OH), 4.65 (s, OCH_2O); IR (neat) 2950–2840, 1500, 1380 cm^{-1}; MS (EI), m/e (relative intensity) 144 (M, 0.05), 143 (2), 113 (67), 99 (53).

5-(Methoxymethoxy)-2-pentenal (20). A mixture of **19** (13.3 g, 92 mmol), pyridine (100 mL), and 5% Pd on $BaSO_4$ (1.3 g) was treated at room temperature with 1 equiv of H_2 to give, after aqueous workup (CH_2Cl_2, $MgSO_4$), 14 g of *cis*-5-(methoxymethoxy)-2-penten-1-ol [^{1}H NMR (60 MHz, $CDCl_3$) δ 5.2–6.0 (m, CH=CH); MS (EI), m/e (relative intensity) 146 (M, 0.02), 84 (100)]. This material was oxidized with excess pyridinium chlorochromate (29 g, 140 mmol), NaOAc (2.3 g, 27 mmol), and CH_2Cl_2 (1.4 L) following the procedure described by Corey.[41] Purification by flash chromatography (1:2 ethyl acetate/hexane) and bulb-to-bulb distillation (oven temperature 85–90 °C; 1.1 mm) gave 8.0 g (60%) of pure **20** as a colorless liquid: 97% pure by capillary GC analysis;[42] ^{1}H NMR (80 MHz, $CDCl_3$) 2.6 (m, =CCH_2), 3.36 (s, OMe), 3.71 (t, J = 6.2 Hz, =CCH_2CH_2), 4.63 (s, OCH_2O), 6.19 (ddt, J = 15.7, 7.7, 1.3 Hz, =CHCHO), 6.89 (dt, J = 15.7, 6.5 Hz, CH=CHCHO), 9.53 (d, J = 7.7 Hz, CHO); d^{25} 1.0558; ^{13}C NMR (63 MHz, $CDCl_3$) 194.0, 155.0, 134.5, 96.7, 65.7, 55.6, 33.7; IR (CCl_4) 1699 cm^{-1}; MS (Cl), m/e 145 (MH^+), 83; MS (EI), m/e 144.080 (144.079 calcd for $C_7H_{12}O_3$).

Diels-Alder Reaction. Preparation of Endo (21) and Exo (22) Adducts. A glass ampule was charged with diene 4[11] (34.0 g, 167 mmol) and enal **20** (7.86 g, 55.0 mmol). The ampule was carefully degassed (evacuate and refill with Ar 4×), sealed, and heated at 110 °C for 1.5 h. Analysis by HPLC[25] (4:1 hexane/ethyl acetate) showed that <10% of **20** remained and that a 9:1 mixture of adducts **21** and **22** was present. The aldehyde epimer[8b,16] of **21** was not detectable by HPLC[25] or 250-MHz ^{1}H NMR analysis. This epimer [^{1}H NMR ($CDCl_3$) 9.75 (br s, CHO)] was isolated from other Diels–Alder reactions and fully characterized. The crude cycloadduct mixture was separated by flash chromatography (2:1 hexane/ethyl acetate). The first fraction yielded 20 g (98 mmol, 80% recovery of the excess) of starting diene 4. A second fraction yielded an impure sample of what is believed to be a Diels–Alder dimer of 4, and a third fraction provided 600 mg (7.6%) of recovered enal **20**. The next fraction afforded 15.7 g (81%) of a 9:1 crystalline mixture[25] of cycloadducts **21** and **22**, which was suitable for use in the subsequent olefination step. Crystallization from ether gave 11.6 g (61%) of this mixture as a white crystalline solid, mp 41 °C. Three crystallizations from ether gave an analytical specimen of endo adduct **21**: contains 4% of **22** by HPLC analysis;[25] mp 46 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 9.67 (s, CHO), 7.35 (m, Ph), 5.68 (m, CH=CH), 5.45 (d, J = 10 Hz, NH), 5.1 (AB q, J = 12 Hz, $\Delta\nu$ = 29.1 Hz, CH_2Ph), 4.62 (s, OCH_2O) 4.57 (m, CHNH), 3.63 (t, J = 6 Hz, CH_2CH_2O), 3.36 (s, OMe); ^{13}C NMR (63 MHz, $CDCl_3$) 202.8, 156.0, 136.6, 128.6, 128.4, 128.3, 128.2, 126.7, 96.6, 67.0, 65.1, 55.4, 54.0, 45.2, 32.8, 28.1, 27.9; IR (CH_2Cl_2) 3441, 1726 cm^{-1}; MS (Cl), m/e 286 (MH^+ − $MeOCH_2OH$). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.96; H, 6.85; N, 3.97.

The last fractions were enriched in exo adduct **22**. Three recrystallizations from ether gave an analytical sample of **22**: mp 91 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 9.63 (d, J = 5 Hz, CHO), 7.33 (m, Ph), 5.70 (m, CH=CH), 5.06 (AB q, J = 12 Hz, $\Delta\nu$ = 28.2 Hz, CH_2Ph), 4.94 (d, J = 9 Hz, NH), 4.66 (m, CHNH), 4.57 (s, OCH_2O), 3.55 (t, J = 6 Hz, CH_2O), 3.33 (s, OMe); ^{13}C NMR (63 MHz, $CDCl_3$) 202.8, 156.0, 136.5, 128.7, 128.33, 128.26, 127.1, 96.7, 67.1, 64.9, 59.3, 55.5, 47.6, 33.9, 30.4, 29.6; IR (CH_2Cl_2) 3436, 1726 cm^{-1}; MS (Cl), m/e 286 (MH^+ −

(41) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2651.
(42) A 25-m SE-30 glass capillary column was used for this analysis.

$MeOCH_2OH$), 135. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.98; H, 6.93; N, 4.04.

Dimethyl 2-Oxo-5-(ethylenedioxy)pentylphosphonate (24). Ethyl 4-hydroxybutanoate[43] (21.6 g, 0.164 mol; prepared in 80% yield at room temperature from γ-butyrolactone, EtOH, and catalytic H_2SO_4) was oxidized with pyridinium chlorochromate (51 g, 0.24 mol) in CH_2Cl_2 (500 mL) containing NaOAc (1.6 g), following the procedure of Corey,[41] to give 17.9 g of crude ethyl 4-oxobutanoate [IR (CH_2Cl_2) 1730 cm^{-1}]. This sample was immediately treated with ethylene glycol (12.8 g, 0.21 mol) and a catalytic amount of camphorsulfonic acid (~100 mg) in refluxing benzene (using a Dean-Stark H_2O separator). Basic workup (10% $NaHCO_3$, CH_2Cl_2, $MgSO_4$) followed by distillation gave 15.8 g (55% from ethyl 4-hydroxybutanoate) of ethyl 4-(ethylenedioxy)butanoate (**23**): bp 117–122 °C (17 mm); ^1H NMR (80 MHz, $CDCl_3$) 4.94 (t, J = 4.2 Hz, OCHO), 4.14 (q, J = 7.2 Hz, OCH_2CH_3), 3.9 (m, OCH_2CH_2O), 1.25 (t, J = 7.2 Hz, Me); IR (CH_2Cl_2) 1730 cm^{-1}.

A modification of the procedure of Corey and Kwiatkowski[26] was used to prepare ketophosphonate **24**. A solution of dimethyl methylphosphonate [5.9 mL, 54 mmol; freshly prepared by the procedure of Ford-Moore and Perry;[44] some samples of commerical (Aldrich) material gave unsatisfactory results] and THF (50 mL) was added at −78 °C to a *mechanically* stirred solution of BuLi (22.3 mL of a 1.95 M solution in hexane, 43.5 mmol). After stirring for 1 h at −78 °C, the white pasty anion was treated dropwise at −78 °C with a solution of ester **23** (3.79 g, 21.8 mmol) and THF (10 mL). The resulting mixture was stirred for 4 h at −78 °C and quenched with saturated aqueous NH_4Cl (100 mL). Isolation with $CHCl_3$ (5 × 200 mL, $MgSO_4$) was followed by concentration at room temperature (0.01 mm) to remove volatile solvents and the bulk of recovered dimethyl methylphosphonate. Purification of the residue by flash chromatography (2:1 hexane/ethyl acetate then 6:3:2 hexane/benzene/ethanol) gave 4.22 g (77%) of pure **24** as a colorless oil, which darkens when left at room temperature: ^1H NMR (250 MHz, $CDCl_3$) 4.92 (t, J = 4.2 Hz, OCHO), 3.9 (m, OCH_2CH_2O), 3.79 (d, J = 11.1 Hz, OMe), 3.12 (d, J = 22.5 Hz, PCH_2), 2.74 (t, J = 7.2 Hz, $COCH_2$), 1.98 (td, J = 7.2, 4.2 Hz, CH_2CH); ^{13}C NMR (63 MHz, $CDCl_3$) 201.2, 103.1, 65.1, 53.2, 53.1, 40.3, 38.1, 27.6; MS (Cl), m/e 253 (MH^+), 191.

Preparation of Enones 25 and 26. Lithium hexamethyldisilylamide (15.5 mL of a 1 M solution in THF, 15.5 mmol) was added dropwise at −20 °C to a solution of phosphonate **24** (4.70 g, 18.6 mmol) and THF (12 mL). The resulting pale yellow solution was stirred at room temperature for 15 min and then cooled to −70 °C. A solution of the crystalline Diels–Alder adduct (5.39 g, 15.5 mmol; a 9:1 mixture of **21** and **22**) and THF (35 mL) was then added dropwise at −70 °C and the resulting solution was allowed to warm to room temperature. The reaction was quenched by pouring into a mixture of 10% aqueous NH_4Cl (100 mL), and the enone product was isolated with ethyl acetate ($MgSO_4$). Flash chromatography (2:1 hexane/ethyl acetate) gave 6.56 g (89.5%) of pure[25] **25** as a colorless oil. Bulb-to-bulb distillation (oven temperature 240 °C, 0.001 mm) provided an analytical specimen of **25**: ^1H NMR (250 MHz, $CDCl_3$) 7.35 (m, Ph), 6.74 (dd, J = 16, 10 Hz, CH=CHCO), 6.19 (d, J = 16 Hz, CH=CHCO), 5.83 (m, CH=CH), 5.08 (s, CH_2Ph), 4.91 (t, J = 4 Hz, OCHO), 4.75 (d, J = 9 Hz, NH), 4.59 (s, OCH_2O), 4.38 (m, CHNH), 3.86 (m, OCH_2CH_2O), 3.56 (m, OCH_2CH_2), 3.34 (s, OMe), 2.65 (t, J = 7 Hz, CH_2CO); ^{13}C NMR (63 MHz, $CDCl_3$) 198.9, 155.6, 145.9, 136.4, 132.3, 129.0, 128.4, 128.0, 126.2, 103.3, 96.3, 66.6, 65.0, 64.8, 55.0, 48.0, 46.4, 33.9, 31.1, 28.7, 27.8; IR (CCl_4) 3450, 2940, 2880, 1728, 1675, 1495 cm^{-1}; MS (Cl), m/e 474 (MH^+). Anal. Calcd for $C_{26}H_{35}NO_7$: C, 65.95; H, 7.45; N, 2.95. Found: C, 66.09; H, 7.47; N, 2.75.

The final fraction of the chromatography was a 1:1 mixture of **25** and **26** (0.61 g, 8.3%). Crystallization from ether/pentane gave pure **26** as white fluffy needles. Two recrystallizations from ether/pentane gave an analytical sample of **26**: mp 89 °C; ^1H NMR (250 MHz, $CDCl_3$) 7.33 (m, Ph), 6.63 (dd, J = 16, 9.2 Hz, CH=CHCO), 6.03 (d, J = 16 Hz, CH=CHCO), 5.79 and 5.58 (m, CH=CH), 5.03 (s, CH_2Ph), 4.92 (t, J = 4.3 Hz, OCHO), 4.58 (s and m, OCH_2O, NH), 4.26 (m, CHNH), 4.0–3.8 (m, OCH_2CH_2O), 3.52 (m, CH_2OCH_2O), 3.34 (s, OMe), 2.68 (m, CH_2CO). Anal. Calcd for $C_{26}H_{35}NO_7$: C, 65.95; H, 7.45; N, 2.95. Found: C, 65.88; H, 7.56; N, 2.93.

3,4,4aβ,5α,6,7,8,8aβ-Octahydro-5-[2-(methoxymethoxy)ethyl]-2-[(3-ethylenedioxy)propyl]quinoline (27). A mixture of **25** (3.02 g, 6.38 mmol), CF_3COOH (12.5 mL), 10% Pd–C (1.5 g), and ethyl acetate was treated at room temperature with H_2 (1 atm). After 15 min, 93% of the theoretical H_2 uptake had occurred. The mixture was then diluted with $CHCl_3$ (1 L), filtered through Celite, and the filtrate was shaken vigorously with 1 N NaOH (3 × 600 mL), H_2O (400 mL), and brine (400 mL) and dried ($MgSO_4$). Concentration gave 1.94 g (94%) of crude **27** as a colorless oil that rapidly yellows if exposed to air: ^1H NMR (250 MHz, $CDCl_3$) 4.92 (t, J = 5 Hz, OCHO), 4.60 (s, OCH_2O), 3.89 (m, OCH_2CH_2O), 3.54 (m, CH_2CH_2O), 3.35 (s, OMe); ^{13}C NMR (63 MHz, $CDCl_3$) 170.6, 104.3, 96.6, 66.0, 65.1, 56.4, 55.3, 37.2, 34.5, 33.3, 32.4, 32.1, 30.1, 29.6, 27.3, 22.3, 21.3; IR (neat) 1658 cm^{-1}. This material was used immediately in the next reaction.

1,2α,3,4,4aβ,5α,6,7,8,8aβ-Decahydro-5-[2-(methoxymethoxy)ethyl]-2-[(3-ethylenedioxy)propyl]quinoline (28). A 1-L flask equipped with an internal thermometer was charged with $LiAlH_4$ (6.62 g, 174 mmol) and absolute ether (500 mL). This mixture was cooled to −19 °C and a solution of imine **27** (1.70 g, 5.23 mmol) and absolute ether (20 mL) was added dropwise with efficient magnetic stirring. The suspension was stirred at −19 °C for 15 h, then was allowed to warm to −5 °C and was quenched by careful addition of ethyl acetate (150 mL). The aluminum salts were hydrolyzed with 1 N NaOH (13 mL) and the gray suspension was allowed to warm to room temperature and stirred for an additional 30 min. After drying ($MgSO_4$), this mixture was filtered through Celite, and the filtrate was concentrated to give 1.71 g (100%) of crude amine as a colorless oil. The 250-MHz ^1H NMR spectrum showed that this material was a 9:1 to 16:1 (range of three experiments) mixture of **28** and **29**, respectively. Spectral data for **28**: ^1H NMR (250 MHz, $CDCl_3$) 4.85 (t, J = 4.2 Hz, OCHO), 4.62 (s, OCH_2O), 4.0–3.8 (m, OCH_2CH_2O), 3.55 (m, CH_2OCH_2O), 3.36 (s, OMe), 3.09 (dt, J = 11.8, 4.2 Hz, CHN), 2.7–2.85 (m, CHN); ^{13}C NMR (63 MHz, $CDCl_3$) 104.4, 96.3, 66.3, 65.8, 64.8 64.7, 55.0, 50.5, 49.2, 40.1, 35.3, 32.5, 30.9, 30.4, 27.5, 25.4, 25.3, 20.9, 20.6; IR (neat) 3400, 1450 cm^{-1}.

Stereoisomer **29** showed a diagnostic[16] ^1H NMR signal at δ 2.87 (narrow m, half-height width ~7 Hz, H_{9a}[15]).

1,2α,3,4,4aβ,5α,6,7,8,8aβ-Decahydro-1-[(2,2,2-trichloroethoxy)carbonyl]-5-[2-(methoxymethoxy)ethyl]-2-[(3-ethylenedioxy)propyl]quinoline (30). Trichloroethyl chloroformate (0.714 mL, 5.23 mm) was added dropwise to a stirred solution of amine **28** (1.70 g, 5.20 mmol), 1,2,2,6,6-pentamethylpiperidine[29] (1.13 mL, 6.28 mmol), and CCl_4 (100 mL). The resulting solution was stirred at room temperature for 12 h. Aqueous workup (ethyl acetate, $MgSO_4$) followed by flash chromatography (2:1 hexane/ethyl acetate) gave 2.21 g (85%) of **30** as a colorless oil, which was a single isomer by 250-MHz ^1H NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) 4.75 (AB q, J = 12 Hz, $\Delta\nu$ = 32 Hz, CH_2CCl_3); ^{13}C NMR (63 MHz, $CDCl_3$) 153.7, 104.3, 96.4, 95.9, 74.9, 66.2, 64.9, 55.1, 51.8, 35.3, 35.1, 32.3, 31.5, 29.4, 23.6, 22.8, 20.0, 19.7; IR (neat) 2930, 2865, 1710, 1405 cm^{-1}, MS (CI), m/e 504 (MH^+), 502 (MH^+); MS (EI), m/e 402.0816 [(402.0819 calcd for $C_{16}H_{25}Cl_3NO_4$, M − $CH_2CH_2(OCH_2CH_2O)$].

1,2α,3,4,4aβ,5α,6,7,8,8aβ-Decahydro-1-[(2,2,2-trichloroethoxy)carbonyl]-5-[2-(methoxymethoxy)ethyl]-2-(5-oxo-3-pentenyl)quinoline (31). A degassed solution of 10% $HClO_4$ and THF (1:1, 100 mL) was added to a stirred degassed solution of **30** (2.20 g, 4.44 mmol) and THF (10 mL). The resulting solution was stirred at room temperature for 2.5 h under an atmosphere of argon. Aqueous workup (ethyl acetate, $MgSO_4$) gave 2.2 g of the corresponding aldehyde [^1H NMR (250 MHz, $CDCl_3$) 9.78 (br s, CHO)]. A 240 mg (0.54 mmol) sample of this material was *immediately* dissolved in $CHCl_3$ (40 mL); (formylmethylene)triphenylphosphorane[30] (590 mg, 1.9 mmol) was added and the resulting dark yellow solution was heated at reflux for 81 h. Concentration and purification of the residue by flash chromatography (4:1 hexane/ethyl acetate) gave 185 mg (75%) of pure **31** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) 9.50 (d, J = 7.8 Hz, CHO), 6.85 (dt, J = 15.7, 6.7 Hz, COCH=CH), 6.13 (dd, J = 15.7, 7.8 Hz, COCH=), 4.75 (AB q, J = 12 Hz, $\Delta\nu$ = 34.8 Hz, CH_2CCl_3), 4.60 (s, OCH_2O), 3.99 (m, CHN), 3.86 (m, CHN), 3.56 (m, CH_2OCH_2O), 3.35 (s, OMe), 2.39 (dd, J = 15.7, 6.7 Hz, CH_2CH=); ^{13}C NMR (63 MHz, $CDCl_3$) 194.1, 157.7, 154.1, 133.6, 96.7, 96.4, 96.1, 75.2, 66.5, 55.5, 51.7, 35.7, 35.6, 30.6, 29.6, 23.8, 20.2; IR (neat) 2930, 1700, 1660 cm^{-1}; MS (Cl), m/e 486 (MH^+), 484 (MH^+), 454 ($MH^+ - CH_3OH$), 452 ($MH^+ - CH_3OH$); MS (El), m/e 402.0808 [402.0819 calcd for $C_{16}H_{25}Cl_3NO_4$, M − $CH_2CH_2CH(OCH_2CH_2O)$].

1,2α,3,4,4aβ,5α,6,7,8,8aβ-Decahydro-5-[2-(methoxymethoxy)ethyl]-2-[(5,5-dimethoxy)-3-pentenyl]quinoline (33). A solution of enal **31** (1.04 g, 2.14 mmol), MeOH (200 mL), and pyridinium *p*-toluenesulfonate[32] was stirred under an argon atmosphere for 1 h. Aqueous workup (ethyl acetate, $MgSO_4$) gave 1.11 g (98%) of crude acetal **32** as a colorless oil [^1H NMR (250 MHz, $CDCl_3$) 5.83 (dt, J = 15.6, 6.7 Hz, CH_2CH=), 5.47 (dd, J = 15.6, 5.3 Hz, =CHCH), 4.70 (d, J = 5.1 Hz, OCHO), 3.35 (s, OMe), 3.30 (s, two OMe)], which was used immediately in the next step. A degassed solution of a 604 mg (1.14 mmol) sample of this material, KOH (10.5 g), 2-propanol (82 mL), and H_2O (102 mL) was heated at reflux for 48 h under an argon atmosphere. Aqueous workup (ethyl acetate, $MgSO_4$) gave 394 mg (97%) of curde **33**: ^1H NMR (250 MHz, $CDCl_3$) 5.81 (dt, J = 15.8, 6.8 Hz, CH_2CH=), 5.46 (dd, J = 15.8,

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5.2 Hz, CH=), 4.72 (d, J = 5.1 Hz, OCHO), 4.60 (s, OCH_2O), 3.55 (m, CH_2OCH_2O), 3.30 (s, two OMe), 3.16 (m, CHN), 2.85 (m, CHN), 2.14 (apparent q, J = 6.8 Hz, CH_2CH=); ^{13}C NMR (63 MHz, $CDCl_3$) 134.1, 126.9, 102.7, 96.0, 77.4, 65.8, 54.7, 52.2, 50.7, 49.4, 35.0, 32.1, 28.1, 25.8, 24.7, 20.1; IR (neat) 3310, 2930, 1580 cm^{-1}; MS (CI), m/e 356 (MH^+), 324 ($MH^+ - CH_3OH$), 226. Amine acetal **33** darkened quickly when exposed to air, and the crude material was used immediately in the next reaction.

2-[1α,2,3,3aα,4,5,5aβ,6α,7,8,9,9aβ-Dodecahydro-6-[2-(methoxymethoxy)ethyl]pyrrolo[1,2-*a*]quinol-1-yl]ethanol (34). A degassed solution of **33** (51 mg, 0.144 mmol), 1 N HCl (1 mL), and THF (3 mL) was maintained at room temperature under an Ar atmosphere for 1 h. A freshly prepared, well-degassed, solution of NaOMe in MeOH (50 mL of a 0.32 M solution) was added. After 1 h at room temperature, $NaBH_4$ (~300 mg, ~55 equiv) was added, and the resulting mixture was stirred for an additional 0.5 h at room temperature. Aqueous workup (ethyl acetate, $MgSO_4$) and purification of the residue on alumina (activity III, 2:1 hexane/ethyl acetate) gave 25.2 mg (56%) of pure **34** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) 4.60 (s, OCH_2O), 4.01 (dt, J = 11.3, 2.4 Hz, C*H*HOH), 3.64 (dt, J = 11.1, 3.6 Hz, CH*H*OH), 3.56 (m, CH_2OCH_2O), 3.36 (s, OMe), 3.26 (m, $C_{9a}H$), 2.55 (m, $C_{3a}H$), 2.05 (m, $CHCH_2OH$); ^{13}C NMR (63 MHz, $CDCl_3$), 96.3, 66.2, 59.6, 56.1, 55.4, 55.1, 50.3, 41.0, 35.9, 32.5, 32.3, 30.8, 30.7, 30.5, 26.3, 26.0, 24.9, 20.1, 16.6; IR (neat) 3420, 2930, 2865, 1450, 1400, 1370, 1320 cm^{-1}; MS (CI), m/e 312 (MH^+), 280 ($MH^+ - CH_3OH$), 266. A chromatography fraction eluted just before **34** was 4 mg (8%) of the primary acetate of **34**: ^1H NMR (250 MHz, $CDCl_3$) 4.60 (s, OCH_2O), 4.10 (m, CH_2OAc), 3.55 (m, CH_2OCH_2O), 3.35 (s, OMe), 3.12 (m, $C_{9a}H$), 2.73 (m, C_1H), 2.5 (m, $C_{3a}H$), 2.04 (s, $COCH_3$); MS (CI), m/e 354 (MH^+), 322 ($MH^+ - CH_3OH$), 294 ($MH^+ - CH_3COOH$), 266.

Conversion of 34 to *tert*-Butyldiphenylsilyl Ether 35. A solution of **34** (125 mg, 0.40 mmol), *tert*-butylchlorodiphenylsilane (125 mg, 0.401 mmol),[35] Et_3N (67 μL, 0.48 mmol), 4-(dimethylamino)pyridine (2 mg, ~4 mol %),[36] and CH_2Cl_2 (2 mL) was maintained overnight at room temperature. Aqueous workup (CH_2Cl_2, $MgSO_4$) and chromatography of the residue on alumina (activity III, CH_2Cl_2) gave 182 mg (83%) of **35** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) 7.68 (m, Ph), 7.40 (m, Ph), 4.63 (s, OCH_2O), 3.82–3.63 (m, OCH_2), 3.58 (m, CH_2OCH_2O), 3.36 (s, OMe), 3.16 (m, $C_{9a}H$), 2.75 (m, C_1H), 2.46 (m, $C_{3a}H$); ^{13}C NMR (63 MHz, $CDCl_3$) 135.7, 134.1, 129.7, 127.8, 96.6, 66.6, 62.2, 55.3, 51.0, 36.2, 32.8, 28.8, 27.3, 27.0, 26.8, 26.6, 26.5, 25.3, 20.3, 19.3, 16.8; IR (neat) 3000, 2930, 1200 cm^{-1}; MS (CI), m/e 550 (MH^+), 266. An analytical sample of the HCl salt was prepared by two recrystallizations from ether/pentane: mp 144–145 °C. Anal. Calcd for $C_{34}H_{52}NO_3Si$: C, 69.64, H, 8.94; N, 2.38. Found: C, 69.71; H, 8.76, N, 2.33.

1α,2,3,3aα,4,5,5aβ,6α,7,8,9,9aβ-Dodecahydro-1-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-6-(2-hydroxyethyl)pyrrolo[1,2-*a*]quinoline (36). A solution of **35** (196 mg, 0.355 mmol), HBr (0.17 mL of a 24% aqueous solution), and dimethoxyethane (2 mL) was heated for 2 h at 50 °C under an argon atmosphere. Basic workup (10% $NaHCO_3$, CH_2Cl_2, $MgSO_4$) followed by purification of the residue on alumina (activity III, 1:1 hexane/ethyl acetate) gave 155 mg (86%) of pure **36**: ^1H NMR (250 MHz, $CDCl_3$) 7.65 (m, Ph), 7.41 (m, Ph), 3.5–3.85 (m, CH_2OSi, CH_2OH), 3.34 (m, $C_{9a}H$), 2.90 (m, C_1H), 2.6 (m, $C_{3a}H$), 1.05 (s, *t*-Bu); ^{13}C NMR (63 MHz, $CDCl_3$) 135.9, 135.2, 129.9, 127.9, 62.3, 61.7, 56.4, 55.3, 50.9, 40.5, 36.1, 35.7, 32.2, 29.3, 26.8, 26.7, 25.7, 20.4, 19.2, 16.7; IR (neat) 3350, 2930, 2860, 1460, 1425 cm^{-1}; MS (CI), m/e 506 (MH^+), 222.

1α,2,3,3aα,4,5,5aβ,6α,7,8,9,9aβ-Dodecahydro-1-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-6-[5-(triisopropylsilyl)-2(*Z*)-penten-4-ynyl]pyrrolo[1,2-*a*]quinoline (38). Alcohol **36** (125 mg, 0.504 mmol) was oxidized, exactly as described by Swern,[37] with the reagent derived from oxalyl chloride (0.48 mL, 0.56 mmol) and Me_2SO (0.08 mL, 1.1 mmol) to afford 125 mg (100%) of crude aldehyde **37**: ^1H NMR (250 MHz, $CDCl_3$) 9.75 (t, J = 2 Hz, CHO), 7.65 (m, Ph), 7.44 (m, Ph), 3.6–3.8 (m, CH_2OSi), 3.12 (m, $C_{9a}H$), 2.75 (m, C_1H); IR (CH_2Cl_2) 1725 cm^{-1}; MS (CI), m/e 504 (MH^+), 220. This sample was used immediately in the next reaction.

A solution of 1,3-bis(triisopropylsilyl)propyne[38] (40 mg, 0.11 mmol) and THF (0.5 mL) was treated dropwise at −20 °C with BuLi (45 μL of a 2.19 M solution in hexane, 0.099 mmol). The slightly yellow anion was stirred for 15 min at −20 °C and cooled to −78 °C, and a solution of crude **37** (35.5 mg, 0.070 mmol) and THF (0.5 mL) was added by drops. The reaction was allowed to slowly warm to room temperature over 12 h. Concentration and purification of the residue on silica gel (9:1 hexane/ethyl acetate, then ethyl acetate) gave 26 mg (55%) of **38** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) 7.68 (m, Ph), 7.40 (m, Ph), 5.90 (8 line m, CH=), 5.60 (d, J = 11 Hz, CH=), 3.72 (m, CH_2OSi), 3.24 (m, $C_{9a}H$), 2.6 (m, CHC=C, C_1H), 2.45 (m, $C_{3a}H$), 2.36 (m, CHC=C), 2.09 (m, $CHCH_2OSi$), 1.09 (m, $CHMe_2$), 1.05 (s, *t*-Bu); ^{13}C NMR (63 MHz, $CDCl_3$) 144.8, 136.2, 135.8, 134.1, 129.7, 127.7, 110.5, 104.2, 94.9, 62.2, 56.3, 55.6, 50.9, 41.1, 40.0, 35.4, 33.8, 32.4, 29.3, 28.9, 28.8, 27.3, 27.0, 26.8, 24.6, 20.3, 20.1, 19.6, 19.4, 18.9, 16.7, 11.9, 11.7, 11.5; IR (CH_2Cl_2) 2940, 2870, 2140, 1465, 1430, 1105 cm^{-1}; MS (CI), m/e 682 (MH^+), 398; MS (EI), m/e 681.467 (681.476 calcd for $C_{44}H_{67}NOSi_2$). The 250-MHz ^1H NMR spectrum showed that this sample was contaminated with ~10% of the corresponding *E* isomer [characteristic signals at δ 5.52 and 6.18].

(±)-Gephyrotoxin (1). A solution of **38** (42.3 mg, 0.062 mmol), *n*-Bu_4NF (0.10 mL of a 1 M solution in THF, 0.10 mmol), and *N*,*N*-dimethylformamide (2 mL) was maintained at room temperature for 40 min under an argon atmosphere and then poured into $CHCl_3$ (50 mL). The organic layer was washed with 10% $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (30:2:0.1 $CHCl_3$/MeOH/12 M NH_4OH) to give an initial fraction (7.2 mg, 41%) that was a 3:1 mixture of **1** and the corresponding *E* isomer, respectively. A subsequent fraction yielded 10.3 mg (58%) of pure (±)-**1** as a colorless oil, which rapidly darkened upon storage: ^1H NMR (250 MHz, C_6D_6) 5.79 (dddd, J = 11, 8.4, 6.7, 0.8 Hz, CH_2CH=),[45] 5.51 (ddt, J = 10.8, 2.3, 1.2 Hz, =CHC≡),[45] 4.07 (dt, J = 10.8, 2.9 Hz, C*H*HOH), 3.77 (dt, J = 10.8, 4.3 Hz, CH*H*OH), 3.46 (dt, J = 12.2, 4.2 Hz, $C_{9a}H$), 3.07 (m, C_1H), 2.95 (d, J = 1.6 Hz, ≡CH), 2.74 (dt, J = 14, 8.5 Hz, C*H*HCH=), 2.42 (m, CH*H*C=), 2.33 (m, $C_{3a}H$), 2.02 (ddt, J = 14.4, 10.2, 4.8 Hz, CH*H*CH_2OH), 1.0–1.8 (m); MS (EI), m/e (relative intensity) 287 (0.5), 286 (0.6), 243 (64), 242 (41), 222 (19). The *trans*-enyne stereoisomer showed characteristic signals in the 250-MHz ^1H NMR spectrum at δ 6.24 (apparent dt, J = 15.5, 7.7 Hz, =C*H*CH_2), 5.58 (ddd, J = 15.9, 3.6, 1.5 Hz, =CHC≡), 2.65 (d, J = 2.2 Hz, ≡CH). Synthetic (±)-**1** cochromatographed with an authentic sample of racemic gephyrotoxin (provided by Dr. Hart) upon TLC analysis on alumina (1:1 hexane/ethyl acetate) and silica gel (1:1 ethyl acetate/MeOH).

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Registry No. (±)-**1**, 75685-48-2; (*E*)-(±)-**1**, 86258-58-4; (*E*)-**4**, 65899-49-2; (±)-**6**, 55950-18-0; (±)-**7**, 86197-24-2; (±)-**10**, 86197-08-2; (±)-**11**, 86258-55-1; **17**, 6261-22-9; **18**, 5582-60-5; **19**, 86197-09-3; **20**, 86197-10-6; (±)-**21**, 86197-11-7; (±)-**22**, 86258-56-2; **23**, 86197-13-9; **24**, 86197-12-8; (±)-**25**, 86197-14-0; (±)-**26**, 86258-57-3; (±)-**27**, 86197-15-1; (±)-**28**, 86197-16-2; (±)-**30**, 86197-17-3; (±)-**30** (aldehyde), 86197-25-3; (±)-**31**, 86197-18-4; (±)-**32**, 86197-26-4; (±)-**33**, 86197-19-5; (±)-**34**, 86197-20-8; (±)-**35**, 86197-21-9; (±)-**36**, 75685-52-8; (±)-**37**, 75648-76-9; (±)-**38**, 86197-22-0; (*E*)-(±)-**38**, 86258-59-5; ethyl 4-hydroxybutanoate, 999-10-0; ethyl 4-oxobutanoate, 10138-10-0; dimethyl methylphosphonate, 756-79-6; 1,3-bis(triisopropylsiyl)propyne, 82192-59-4; $ClCH_2OMe$, 107-30-2; 1-pentynyllithium, 18643-50-0; benzyl bromide, 100-39-0; trichloroethyl chloroformate, 17341-93-4; *tert*-butylchlorodiphenylsilane, 58479-61-1.

(45) Multiplet resolved by resolution enhancement.