ditions. The NMR and IR were consistent with the assigned structure.

The established requirement of 3 equiv of LDA/equiv of MoO_5·HMPA seems to indicate that lithium diisopropylamide is serving in a ligand capacity with molybdenum complex. The utilization of 1 or 2 equiv of LDA/equiv of MoO_5·HMPA results in recovered starting material while 4 equiv of LDA gives indole (benzofuran) in reduced yields.

The general procedure for the synthesis of an indole or benzofuran was as follows: A 50-mL, three-necked round-bottomed flask equipped with a nitrogen inlet tube and a Teflon magnetic stirring bar was charged with γ-sultam 1 (1–5 mmol). The γ-sultam was dissolved in anhydrous THF (8–15 mL) and cooled to −78 °C with the aid of a dry ice/acetone bath. *n*-Butyllithium (1 equiv) in hexane was added via syringe, and the solution was stirred at −78 °C for 1 h. In a second 50-mL flask equipped in the same manner was placed 1.1 mmole of MoO_5·HMPA (previously dried from MoO_5·HMPA·H_2O via P_2O_5/0.2 mm, 36 h) and dissolved in anhydrous THF (5–10 mL). The solution was cooled to −78 °C prior to the addition of LDA (3.3 mmol). The MoO_5·HMPA–LDA solution was added to the γ-sultam solution via a double-ended needle. The reaction was stirred at −78 °C for 2 h. The solution was allowed to warm to room temperature, quenched with water (10 mL), and brought to 45 °C for 1 h. Saturated sodium sulfite (10 mL) was added and the reaction diluted with water (40 mL). The reaction mixture was extracted with diethyl ether (2 × 50 mL) and dried ($MgSO_4$), and the diethyl ether was removed in vacuo. The crude product was purified by column chromatography (silica gel eluted with petroleum ether).

Registry No. 1 (X = CH_3N; Y = H), 64825-94-1; 1 (X = CH_3N; Y = CH_3), 64825-96-3; 1 (X = CH_3)$_3$CN; Y = CH_3), 78307-50-3; 1 (X = *p*-$CH_3C_6H_4N$; Y = CH_3), 78307-51-4; 1 (X = CH_3N; Y = C_6H_5), 64826-00-2; 1 (X = *p*-$CH_3C_6H_4N$; Y = CH_3CH_2), 78307-52-5; 1 (X = *p*-$CH_3C_6H_4N$; Y = *p*-ClC_6H_4), 78307-53-6; 1 (X = *p*-$CH_3OC_6H_4N$; Y = $(CH_3)_2CH$, 78307-54-7; 1 (X = *p*-BrC_6H_4N; Y = $(CH_3)_2CH$), 78307-55-8; 1 (X = *p*-$CH_3C_6H_4N$; Y = CH_3SO_2), 78307-56-9; 1 (X = O; Y = C_6H_5), 42224-35-1; 1 (X = O; Y = *p*-$CH_3C_6H_4$), 78307-57-0; 2 (X = CH_3N; Y = CH_3), 78307-58-1; 3 (X = CH_3N; Y = H), 603-76-9; 3 (X = CH_3N; Y = H) picrate, 29052-34-4; 3 (X = CH_3N; Y = CH_3), 875-79-6; 3 (X = $(CH_3)_3CN$; Y = CH_3), 46250-15-1; 3 (X = *p*-$CH_3C_6H_4N$; Y = CH_3), 78307-59-2; 3 (X = CH_3N; Y = C_6H_5), 3558-24-5; 3 (X = *p*-$CH_3C_6H_4N$; Y = CH_3CH_2), 78307-60-5; 3 (X = *p*-$CH_3C_6H_4N$; Y = *p*-Cl_6H_4), 78307-61-6; 3 (X = *p*-$CH_3OC_6H_4N$; Y = $(CH_3)_2CH$), 78307-62-7; 3 (X = *p*-BrC_6H_4N; Y = $(CH_3)_2CH$), 78307-63-8; 3 (X = *p*-$CH_3C_6H_4N$; Y = CH_3SO_2), 78307-64-9; 3 (X = O; Y = C_6H_5), 1839-72-1; 3 (X = O; Y = *p*-$CH_3C_6H_4$), 25664-48-6.

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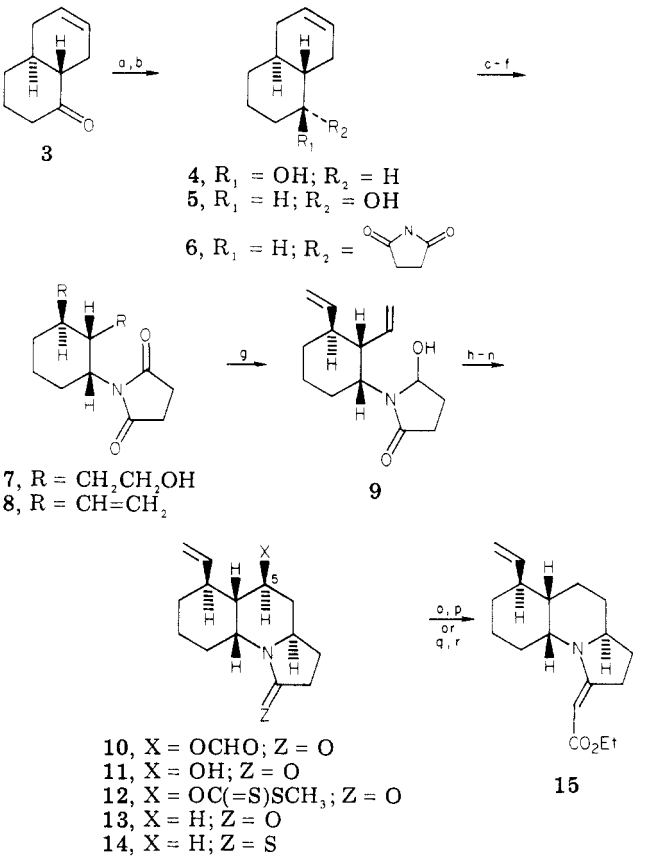
Received April 22, 1981

A Synthesis of (±)-Gephyrotoxin

Summary: A formal total synthesis of the Dendrobatid alkaloid gephyrotoxin (1) is described.

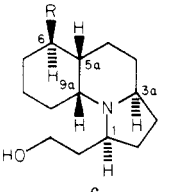
Sir: Gephyrotoxin (1), a component of a skin secretion produced by the poison-dart frog, *Dendrobates histrionicus*,[1] has been the objective of several synthetic studies.[2-5]

Scheme I[a]



[a] (a) $LiAlH_4$, THF, −70 °C; (b) PPh_3, $EtO_2CN{=}NCO_2Et$, $C_4H_5NO_2$; (c) O_3, CH_3OH, −70 °C; (d) $NaBH_4$, CH_3OH, −70 °C → 25 °C; (e) *o*-$NO_2PhSeCN$, *n*-Bu_3P, THF; (f) H_2O_2, 25 °C; (g) *i*-Bu_2AlH, $PhCH_3$, −65 °C; (h) HCOOH, 25 °C, 30 min; (i) 1.5 equiv of NaOH, CH_3OH-H_2O; (j) NaH, imidazole, THF, 60 °C; (k) CS_2; (l) CH_3I; (m) *n*-Bu_3SnH, toluene, reflux, 16 h; (n) $(pMeOPhPS_2)_2$, toluene, 100 °C, 10 min; (o) $BrCH_2CO_2Et$, Et_2O; (p) Ph_3P, Et_3N, CH_2Cl_2; (q) CH_3I, Et_2O; (r) $EtO_2CCHCOOMg$, DMF, 60 °C, 2 h.

Most notably, the groups of Kishi[4] and Overman[2] have reported syntheses of (±)-1 and perhydrogephyrotoxin (2), respectively. We have now completed a formal synthesis of (±)-1, the details of which are outlined herein.



1, R = $CH_2CH{=}^{c}CHC{\equiv}CH$
2, R = $CH_2CH_2CH_2CH_2CH_3$

Our approach to the stereochemical problems presented by gephyrotoxin focused on (i) establishing the relative stereochemistry at the three contiguous asymmetric centers (C-6, C-5a, C-9a), (ii) transmitting the proper stereochemistry to C-3a using an *N*-acyliminium ion cyclization,[6,7] and

(1) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128.
(2) Overman, L. E.; Fukaya, C. J. *J. Am. Chem. Soc.* **1980**, *102*, 1454.
(3) Habermehl, G. G.; Thurav, O. *Naturwissenschaften* **1980**, *67*, 193.
(4) Fugimoto, R.; Kishi, Y.; Blount, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7154.
(5) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367.
(6) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163.

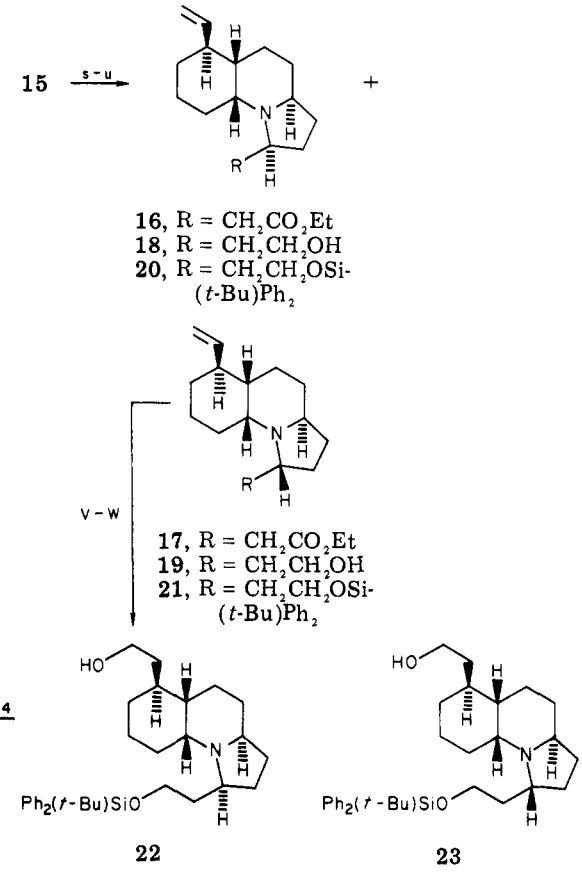
0022-3263/81/1946-3576$01.25/0

(iii) appending the C-1 side chain in a stereocontrolled fashion. Our synthesis of the required *N*-acyliminium ion precursor **9** is outlined in Scheme I. Treatment of cyclohexenone with 1,3-butadiene in the presence of aluminum trichloride gave a 70% yield of crystalline enone **3** (mp 45–47 °C).[8] Stereoselective reduction of **3** was accomplished with lithium aluminum hydride at −70 °C to give alcohol **4** (83%, mp 64–67 °C) along with 9% of isomeric alcohol **5**.[9] Treatment of alcohol **4** with succinimide, triphenylphosphine, and diethylazodicarboxylate[10] gave imide **6** in a 62% yield.[11] Thus in three steps the stereochemistry at the incipient C-6, 5a, and 9a centers was established. Ozonolysis of imide **6** followed by a carefully monitored reductive workup with sodium borohydride gave diol **8** (mp 120–122 °C) in an 81% yield. Treatment of diol **7** with *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine in tetrahydrofuran[12] followed by oxidation of the resulting bis selenide with hydrogen peroxide[13] gave diene **8** (one-pot, 76%).[14] Reduction of **8** with diisobutylaluminum hydride gave carbinolamide **9** (79%, mp 62–77 °C).[15]

The ^{1}H NMR spectrum of **8** implies that it adopts a chair conformation in which the two vinyl groups occupy axial sites on the cyclohexane ring.[16] This observation suggested that no stereochemical problems would be encountered in the ensuing cyclization.[5,7] Treatment of carbinolamide **9** with formic acid gave tricyclic lactam **10** as a crystalline solid (79%, mp 116–119 °C). Our stereochemical assignment for lactam **10** was made on the basis of spectral data and the assumption that the stereochemistry at carbons 6, 5a, and 9a remained intact during the cyclization.[7] The undesired C-5 functionality was removed by using the excellent procedure of Barton.[17] Thus, hydrolysis of formate **10** gave alcohol **11** (99%, mp 102–104 °C), which was converted to xanthate **12** (92%, mp 145–147 °C). Treatment of **12** with tri-*n*-butyltin hydride in refluxing toluene gave lactam **13** (68%, mp 45–50 °C).[18]

The carbons required to construct the C-1 side chain were introduced as follows. Treatment of lactam **13** with Lawesson's reagent[19] gave thiolactam **14** (95%, mp 85–89 °C). Thiolactam **14** was alkylated with ethyl bromoacetate and the resulting alkylmercaptoalkylideniminium salt was treated with triethylamine and triphenylphosphine to give vinylogous urethane **15** (84%, mp 99–101 °C).[20] In an alternative procedure, thiolactam **14** was alkylated with iodomethane and the resulting salt was treated with the dibasic magnesium salt of ethyl hydrogen malonate to afford **15** in a 75% yield.[21]

Scheme II[a]



[a] (s) $NaBH_3CN$, CH_3OH, pH 4; (t) $LiAlH_4$, THF; (u) *t*-$BuPh_2SiCl$, DMF, imidazole; (v) disiamylborane, THF; (w) NaOH, H_2O_2.

A formal synthesis of gephyrotoxin was completed as outlined in Scheme II. Vinylogous urethane **15** was reduced with sodium cyanoborohydride[22] to give a separable mixture of amino esters **16** (60%, mp HCl salt 125–129 °C) and **17** (29%, mp HCl salt 175–177 °C). Treatment of **16** with lithium aluminum hydride followed by protection of the resulting alcohol **18** as its *tert*-butyldiphenylsilyl ether[23] gave amino olefin **20** in a 90% yield. Hydroboration of **20** with disiamylborane[24] followed by oxidation gave alcohol **22** (63%, mp 95–102 °C). Amino alcohol **22** was identical (TLC, ^{1}H NMR, IR) with a sample generously provided by Professor Yoshito Kishi and was easily distinguished (TLC, ^{1}H NMR) from amino alcohol **23**, prepared in an analogous fashion from amino ester **17**. Since **22** has previously been converted to (±)-**1** in an overall yield of 45%,[4] the sequence described herein constitutes a total synthesis of gephyrotoxin.[25-28]

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(8) Fringvelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Synth. Commun.* **1979**, *9*, 391.
(9) Alcohol **4** was crystallized from the crude reaction mixture in a 75% yield. The mother liquor was chromatographed to afford **5** and additional **4**. When the reduction was performed at room temperature, a 92% yield of a 4.4:1 mixture of **4**:**5** was obtained.
(10) Mitsunobu, D.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.
(11) About 20% of alcohol **5** was also obtained.
(12) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485; Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717.
(13) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947.
(14) In a single reaction we have prepared 20.0 g diene **8** via this reaction sequence.
(15) Winterfeldt, E. *Synthesis* **1975**, 617.
(16) The incipient C-9a hydrogen in **8** appeared as a doublet of triplets (J = 12, 4.5, 4.5 Hz) at δ 4.23. The same hydrogen in diol **7** also appeared as a doublet of triplets (J = 12, 4, 4 Hz) at δ 4.22.
(17) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(18) One small scale experiment (1.0 g of **12**) gave a 78% yield of lactam **13**.
(19) Pederson, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.
(20) Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710; Yamaguchi, H. *Chem. Abstr.* **1972**, *78*, P29617.
(21) This method represents an alternative to the Eschenmoser method of vinylogous urethane formation from *N*-alkylthiolactams: Tsai, Y.-M.; Gugelchuk, M. M.; Hart, D. J. *J. Org. Chem.* **1981**, in press.
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(24) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 1241.
(25) We are currently examining alternative methods of converting vinylogous urethane **15** to gephyrotoxin which proceed with higher stereoselectivity at C-1 and use different methods for appending the ene–yne unit. The results of these studies will appear in the full account of our work.
(26) All compounds reported herein have ^{1}H NMR, IR, mass spectral, exact mass, and in some instances ^{13}C NMR spectra consistent with the assigned structures. Acceptable combustion analyses were obtained for **4**, **7**, **9**, **10**, **12**, and **15**.

Registry No. 1, 75685-48-2; 3, 78341-47-6; 4, 78341-48-7; 5, 78341-49-8; 6, 78308-01-7; 7, 78308-02-8; 8, 78308-03-9; 9, 78308-04-0; 10, 78308-05-1; 11, 78308-06-2; 12, 78308-07-3; 13, 78308-08-4; 14, 78308-09-5; 15, 78308-10-8; 16, 78308-11-9; 16·HCl, 78341-50-1; 17, 78392-00-4; 17·HCl, 78418-44-7; 18, 78308-12-0; 19, 78341-51-2; 20, 78328-74-2; 21, 78392-01-5; 22, 75685-52-8; 23, 78392-02-6; cyclohexenone, 930-68-7; 1,3-butadiene, 106-99-0.

Supplementary Material Available: ^{1}H NMR spectra of all new compounds described herein (21 pages). Ordering information is given on any current masthead page.

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Received June 16, 1981

(27) I thank Dr. Chuck Cottrell and Mr. Richard Weisenberger for their assistance in obtaining ^{13}C NMR and mass spectra, respectively.
(28) Financial support from donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (GM27674-01) is gratefully acknowledged.