reaction solvent was added. Then the temperature was adjusted and the epoxide added. Reactions were quenched with 1 M acetic acid in ether. Analyses of the resulting mixtures were performed by integration of ^{13}C NMR signals of the γ-carbons recorded under conditions where these should be an accurate measure of concentration.[10,11] Comparison of these results with GLC integration in two cases gave identical (±2%) diastereomeric ratios. The results are shown in Table I.

As previously observed,[7,9] the addition of carboxamide α-anions to terminal epoxides proceeded readily at 0 °C. The product γ-hydroxy amides were highly crystalline compounds. In every case where significant asymmetric induction was observed (see below), the major diastereomer crystallized from the product mixture (after the unreacted amide had been removed by distillation under reduced pressure) and could be recrystallized to high purity. Although the product N,N-disubstituted γ-hydroxy amides with large groups on nitrogen (from amides c–g, Scheme I) hydrolyzed with more difficulty than did the *N,N*-dimethyl-γ-hydroxy amides, treatment of the former products with 6 M HCl at 50 °C for 72 h gave γ-butyrolactones in moderate yields. The major diastereomer produced from the reaction of **1c** and **2a** yielded only *trans*-2,4-dimethyl-γ-butyrolactone on hydrolysis[12] in agreement with the mechanism proposed above. This lactone was identified by comparison of its ^1H NMR spectra with the distinctly different spectra reported[13] for the authentic cis and trans isomers. Thus, the major diastereomeric product had the erythro configuration **3**.

Significant asymmetric induction (diastereomeric ratios ≥2) was observed only when the substituents on nitrogen were large (see Table I, entries 1–4 and 7) probably because only then was the amide group significantly larger than methyl. The stereoselectivity obtained increased markedly as the temperature was lowered (entries 3–6), and excellent selectivity was obtained at −78 °C. Unfortunately, the rate of reaction was very slow at this temperature. The reaction was more stereoselective in ether than in THF (compare entries 4 and 8), and the addition of cation complexing reagents lowered the stereoselectivity (compare entries 3 and 4 with 9 and 10, respectively). These results suggest that the structure of the anion is closer to a contact ion pair than a solvent-separated ion pair in ether[14] than under the other conditions examined. Contact ion pairs are known to be larger than solvent separated ion pairs.[14] Stereoselectivity for the erythro product increased as the size of the R group on the epoxide increased (entries 4, 11–14) consistent with increased differentiation between R_M and R_S (see structure I) and perhaps also between R_M and R_L. When the size of R_M was increased (entries 4 and 15–17), the stereoselectivity initially increased (for R_M = ethyl), but further gain in size brought decreased stereoselectivity. These observations suggest a conflict between increased differentiation between R_M and R_S and decreased differentiation between R_M and R_L as R_M is increased in steric bulk.

The results herein indicate that additions of carbanions to monosubstituted epoxides constitute a promising approach to the difficult problem of 1,3 asymmetric induction. Investigations of other carbanion stabilizing groups are in progress to extend the usefulness of the method.

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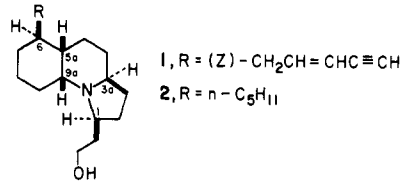
(10) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden; London, 1976; pp 264–271.
(11) ^{13}C NMR spectra were recorded with 35° pulse angles and ≥1.5-s pulse intervals.
(12) Acid-catalyzed equilibration of the two diastereomers would have given about equal amounts of both compounds.[13]
(13) Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1480–1492.
(14) House, H. O.; Auerback, M. G.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514–522.

Short Total Synthesis of (±)-Perhydrogephyrotoxin

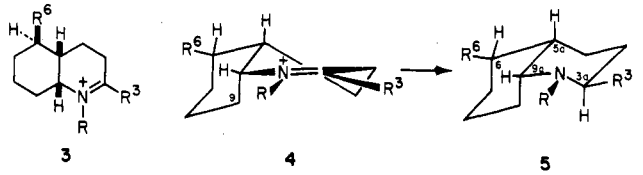
Summary: Preparation of the dendrobatid poison-frog alkaloid toxin (±)-perhydrogephyrotoxin from benzyl *trans*-1,3-butadiene-1-carbamate is described; the synthesis features the stereoselective reduction of *cis*-octahydroindole **9** from the sterically hindered concave face.

Sir: Gephyrotoxin (1), the parent member of a new class of skin alkaloids from tropical poison frogs of the genus *Dendrobates*, was first described by Daly, Witkop, and co-workers in 1977.[1] Last year we reported[2] a stereoselective total synthesis of (±)-perhydrogephyrotoxin (**2**), and



more recently Kishi and co-workers[3] recorded the first total synthesis of (±)-gephyrotoxin. In conjunction with our interest in the biological activity[1,4] of this series, we have been investigating simplified approaches to gephyrotoxin and gephyrotoxin analogues. In this communication we describe a new concise approach to these alkaloids and specifically report a short, stereocontrolled total synthesis of (±)-perhydrogephyrotoxin.

Our preliminary investigations in the gephyrotoxin area[2,5] indicated that it might be possible to reduce bicyclic iminium ion **3** (R = electrophilic metal species) from the



sterically more congested concave α face. We anticipated that iminium ion **3** would be preferentially reduced via a transition-state conformer related to **4**, since the alternate conformer would be destabilized by $A^{1,2}$ interactions between R and C-9.[6] A stereoelectronic preference[7] for initial

(1) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. *Helv. Chim. Acta* **1977**, *60*, 1128. Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163.
(2) Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454.
(3) Fujimoto, R.; Kishi, Y.; Blount, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7154.
(4) Mensah-Dwumah, M.; Daly, J. W. *Toxicon* **1978**, *16*, 189.
(5) Unpublished studies of Dr. Mitsunori Hashimoto.
(6) Cf.: Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

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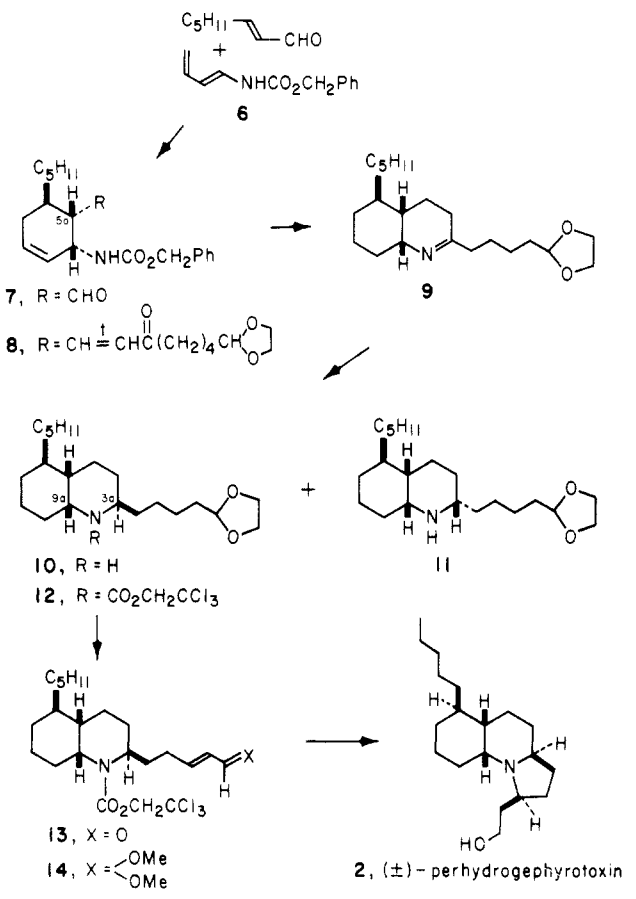
Scheme I



trans-diaxial alignment of an entering hydride nucleophile and the developing nitrogen lone pair would then lead to decahydroquinoline **5**. The total synthesis of (±)-perhydrogephyrotoxin by this approach is summarized in Scheme I.

Endo cycloadduct **7** (^{1}H NMR δ 9.64) was formed with good stereoselectivity (endo/exo ratio >8, HPLC analysis) from the Diels–Alder reaction of benzyl *trans*-1,3-butadiene-1-carbamate (**6**)[8] and *trans*-2-octenal;[9] however, this conversion was seriously complicated by competing epimerization[10] of adduct **7** at C-5a.[11] The cycloaddition was best carried out for 3 h at 110 °C (50% conversion), and the mixture of **7** and diene **6** remaining after the removal (in vacuo) of unreacted octenal was directly olefinated by treatment in THF (−50 to +25 °C) with dimethyl 2-oxo-7-(ethylenedioxy)heptyl phosphonate[12] to give, after purification on silica gel, enone **8**[13] (IR 1730, 1680, 1630 cm^{-1}) in 49% yield based on converted diene. Catalytic hydrogenation (10% Pd/C, EtOAc) of **8** could be stopped at the keto ammonium salt by conducting the reaction in the presence of a large excess of CF_3COOH. Filtration and subsequent partitioning of the filtrate between hexane and 1 N NaOH afforded imine **9**[13] (C=N: IR 1660 cm^{-1}; ^{13}C NMR δ 170.6) in essentially quantitative yield. Treatment of imine **9** in ether at −15 °C with ~25 equiv of powdered $LiAlH_4$ gave *cis*-decahydroquinolines **10** (maleate salt, mp 125–126 °C)[13] and **11** (maleate salt, mp 143–144 °C)[13] in a ~9:1 ratio.[14] Stereochemical assignments followed directly[2,10] from NMR spectra [**10**: ^{1}H NMR δ 3.06 (dt, J = 11.8 and 4.0 Hz, C-9a H); ^{13}C NMR δ 50.9 and 49.6 (C-3a and C-9a). **11**: ^{1}H NMR δ 2.88 (br s, $W_{1/2}$ = 6 Hz, C-9a H); ^{13}C NMR δ 58.5 and 56.4 (C-9a and C-3a)].[11] Acylation of this mixture with 2,2,2-trichloroethyl chloroformate (1,2,2,6,6-pentamethylpiperidine, 1.1 equiv; CCl_4; room temperature) followed by purification on silica gel gave **12**[13,15] [IR 1704 cm^{-1}; ^{13}C NMR δ 52.0 and 51.3 (C-3a and C-9a)] in ~80% overall yield from **8**. A variety of hydrides and hydride–Lewis acid mixtures were examined in an attempt to increase the stereoselectivity of the **9** → **10** conversion; however, all proved to be inferior to $LiAlH_4$. The reduction of imine **9** with $LiAlH_4$ to afford primarily **10** should be contrasted with hydrogenation of **9** in the presence of 1 equiv of HCl[10] or reduction of **9** with $NaBH_4$ in MeOH which gave **11** with high (>20:1) stereoselectivity.

Deacetalization of carbamate **12** (4:3:2 THF–HOAc–1 N HCl, room temperature) followed by enol silylation[16,17] (trimethylsilyl triflate, 1.5 equiv; *i*-Pr_2NEt, 2.0 equiv; toluene; room temperature; 5 h; excess silyl triflate quenched with Et_2NH) and oxidation by the procedure of Saegusa and Ito[18] ($Pd(OAc)_2$, 1.5 equiv; 1:1 CH_3CN–DMF; 0.5 h; room temperature) gave enal **13**[13,15] [^{1}H NMR δ 9.50 (d, J = 8.1 Hz)] in 93% yield. Although **13** could be directly converted to **2**, the efficiency of this conversion was better if **13** was initially protected by conversion[2] (MeOH; pyridinium *p*-toluenesulfonate,[19] 0.05 equiv; room temperature; 2 h) to the dimethyl acetal **14**.[13,15] Treatment of **14** (in 4:1 THF–1 M NH_4OAc)[20] with ~10 equiv of Zn/Pb couple[21] for 1 h at room temperature afforded the deprotected amine acetal in excellent yield. This crude material was immediately dissolved in THF and converted into (±)-perhydrogephyrotoxin by sequential treatment at room temperature with (i) 2 equiv of 1 N HCl for 1 h, (ii) ~20 equiv of 1% NaOMe in MeOH for 1 h,[22] and (iii) excess $NaBH_4$ for 0.5 h. Purification on silica gel (30:1:0.1 $CHCl_3$–2-propanol–NH_4OH) gave pure[23] (±)-perhydrogephyrotoxin (**2**) in 46% overall yield from **13**; synthetic **2** was identical with a sample prepared from natural gephyrotoxin[24] by comparison of 250-MHz ^{1}H NMR ($CDCl_3$)

(7) Cf.: Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645.
(8) Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Org. Synth.* **1979**, *59*, 1.
(9) Crombie, L. *J. Chem. Soc.* **1955**, 1007.
(10) Cf: Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179.
(11) The numbering used for all intermediates corresponds to that of gephyrotoxin; see ref 1 and structure **1**.
(12) Prepared similarly to compound **24** of ref 10.
(13) Satisfactory spectral (250-MHz ^{1}H NMR, ^{13}C NMR, IR) and analytical (high-resolution mass spectral or combustion analysis) data were obtained for new compounds **8**–**14** reported in Scheme I.
(14) This ratio was determined by integrating the signals for the C-9a hydrogens in the 250-MHz ^{1}H NMR spectrum. The **10**/**11** ratio varied from 7:1 to 13:1 over a number of runs.
(15) It was extremely difficult to remove all of the C-3a[11] epimer, and consequently this sample was contaminated with ~5% of this isomer.
(16) Cf.: Simchen, G.; Kober, W. *Synthesis* **1976**, 259.
(17) This method of aldehyde enol silylation proved considerably more efficient in our hands than classical procedures (e.g., Me_3SiCl/Et_3N/DMF: House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324). The combination of this enol silation procedure with the Saegusa–Ito oxidation method[19] provides an excellent, high-yielding procedure for converting a saturated aldehyde to a conjugated enal.
(18) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(19) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(20) Just, G.; Grozinger, K *Synthesis* **1976**, 457.
(21) Prepared from 70.2 g of zinc and 11.0 g of yellow lead oxide by a procedure developed by George Lenz and L. N. Nysted of the Searle Corp. We greatly appreciate Dr. Lenz suggesting this couple to us and providing us with the details of its preparation.
(22) Michael ring closure of the enal was considerably more stereoselective (**2** and its C-1 epimer[2] were produced in a 20:1 ratio)[23] than the related[2] cyclization of the unsaturated ester.
(23) A 12-m, SE-30, glass capillary column (4000 plates/m) was used for this analysis.
(24) Kindly provided by Dr. John Daly of the NIH.

and ^{13}C NMR (C_6D_6) spectra and capillary GC[23] retention times.

The procedure recorded here achieves a *practical* total synthesis of (±)-perhydrogephyrotoxin in 13 total steps (six isolated intermediates) and an overall yield of ~15% from benzyl *trans*-1,3-butadiene-1-carbamate.

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Supplementary Material Available: Spectra (250-MHz ^1H NMR, ^{13}C NMR, IR) for new compounds 8–14 described in this paper (23 pages). Ordering information is given on any current masthead page.

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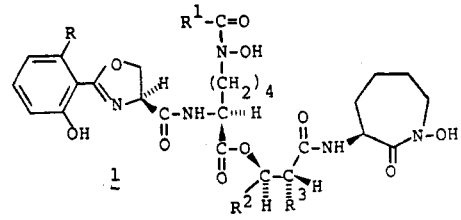
Mycobactins: Synthesis of (−)-Cobactin T from ϵ-Hydroxynorleucine

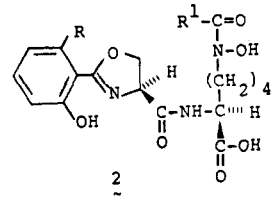
Summary: The synthesis of (−)-cobactin T is described, the key step being ring closure between C_6 and the hydroxamate N of α-*N*-(*tert*-butoxycarbonyl)-ϵ-hydroxynorleucine *O*-benzylhydroxamate.

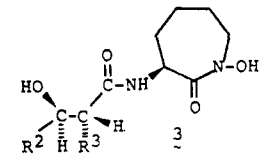
Sir: Mycobactin T (1) is one of the simplest members of the family of mycobactins discovered and characterized by Snow.[1-3] These compounds are naturally occurring growth factors of *Mycobacteria*. They are exceptionally potent chelators of ferric ion. This property, coupled with a high lipophilicity, suggests that the mycobactins are ferric ionophores firmly imbedded in the lipid sheath of *Mycobacteria*.[3-5]

All of the known mycobactins can be saponified to yield two products, mycobactic acid (2) and cobactin (3). Each of these contains a hydroxamic acid residue derived from *N*-hydroxylysine. In mycobactic acid the residue is acyclic whereas in cobactin it is incorporated in a seven-membered lactam ring (the cobactin ring system). These two residues, and a 2-(2-hydroxyphenyl)oxazoline residue, comprise the hexadentate ferric chelation system. Lipophilicity is endowed by a long hydrocarbon chain which, depending on the type of mycobactin, may be either on the acyl portion (1, R^1) of the acyclic hydroxamic acid or on the β-hydroxy acid (1, R^2) which links the cobactin ring system to the rest of the molecule.

Several of the *Mycobacteria* are dangerous pathogens, and the suggestion that certain synthetic analogues of the mycobactins may specifically inhibit the growth of *Mycobacteria* spurred explorations into methods of synthesis







of the various mycobactin fragments.[6-8] The application of a single retrosynthetic step to a mycobactin yields the two known saponification products, mycobactic acid and cobactin (2 and 3). Several of the mycobactic acids and cobactins, including cobactin T, have been isolated and characterized by Snow's group[1,2] although none have previously been synthesized. The synthesis of 2-(2-hydroxyphenyl)-2-oxazoline-4-carboxylic acid was achieved,[6] but all attempts at construction of the cobactin ring system resulted in poor or no yield of hypothetical precursors to the actual target molecule.[7,8]

Our design (Scheme I) for the synthesis of the cobactin ring system originated in part from results obtained earlier in this laboratory concerning β-lactam syntheses.[9] By analogy to the dehydrative cyclization of a suitably α-N-protected *O*-alkylserine hydroxamate to give a four-membered *N*-alkoxy lactam, an α-N-protected *O*-alkyl hydroxamate of ϵ-hydroxynorleucine might yield the seven-membered *N*-alkoxy lactam in suitably protected form. The precursor 6 was required to test the cyclization reaction. The synthesis of 6 began with ϵ-hydroxynorleucine (4) prepared by the method of Gaudry.[10] The amino acid was enzymatically resolved,[11] and the L component was isolated in 76% yield; $[\alpha]^{25}_D$ +22.9 ± 1° (*c* 2, 6 N HCl) [lit.[11] $[\alpha]^{21}_D$ +22.8° (*c* 2, 5 N HCl)]. The L amino acid was stirred with 1 equiv of Et_3N and 1.2 equiv of di-*tert*-butyl dicarbonate in THF/H_2O (1:1) at room temperature overnight to yield 96% (80% after recrystallization) of α-*N*-(*tert*-butoxycarbonyl)-L-ϵ-hydroxynorleucine (5): mp 112–113 °C; $[\alpha]^{23}_D$ −6.36 ± 0.8° (*c* 7.3, MeOH). Conversion to the *O*-benzyl hydroxamate 6 was accomplished by treating an aqueous solution at pH 4.5 with a slight excess of *O*-benzylhydroxylamine hydrochloride followed by 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide and maintaining the pH at 4.5 with stirring at room temperature for 0.5 h. The product was purified by acid/base extraction to give a colorless glass which slowly solidified: 80% yield; $[\alpha]^{23}_D$ −31.2 ± 1.7° (*c* 11, MeOH).

The hydroxamate was cyclized in THF by using a slight excess of PPh_3 and diethyl azodicarboxylate (DEAD). The products were separated by chromatography and recrystallized from hexane. Pure 8 and a mixture of 7 and 9 were

(1) Snow, G. A. *Biochem. J.* **1965**, *97*, 166.
(2) White, A. J.; Snow, G. A. *Biochem. J.* **1969**, *108*, 785.
(3) Snow, G. A. *Bacteriol. Rev.* **1970**, *34*, 99.
(4) Ratledge, C. *Biochem. Biophys. Res. Commun.* **1971**, *45*, 856.
(5) Ratledge, C.; Marshall, B. J. *Biochim. Biophys. Acta* **1972**, *279*, 58.
(6) Black, D. St. C.; Wade, M. J. *Aust. J. Chem.* **1972**, *25*, 1797.
(7) Black, D. St. C.; Brown, R. F. C.; Wade, A. M. *Aust. J. Chem.* **1972**, *25*, 2429.
(8) Black, D. St. C.; Brown, R. F. C.; Wade, A. M. *Aust. J. Chem.* **1972**, *25*, 2155.
(9) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026.
(10) Gaudry, R. *Can. J. Res., Sect. B* **1948**, *26*, 387.
(11) Bodansky, M.; Martinez, J.; Priestly, G. P.; Gardner, J. D. Mutt, V., *J. Med. Chem.* **1978**, *21*, 1030.

0022-3263/81/1946-2835$01.25/0