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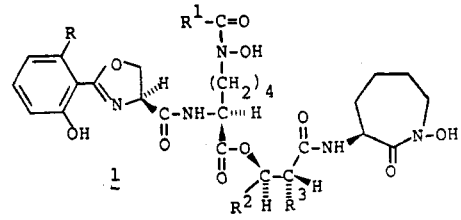
Mycobactins: Synthesis of (−)-Cobactin T from ϵ-Hydroxynorleucine

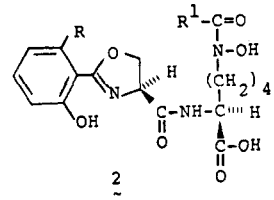
Summary: The synthesis of (−)-cobactin T is described, the key step being ring closure between C_6 and the hydroxamate N of α-*N*-(*tert*-butoxycarbonyl)-ϵ-hydroxynorleucine *O*-benzylhydroxamate.

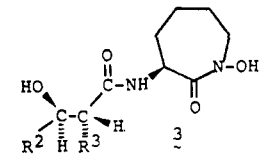
Sir: Mycobactin T (1) is one of the simplest members of the family of mycobactins discovered and characterized by Snow.[1-3] These compounds are naturally occurring growth factors of *Mycobacteria*. They are exceptionally potent chelators of ferric ion. This property, coupled with a high lipophilicity,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

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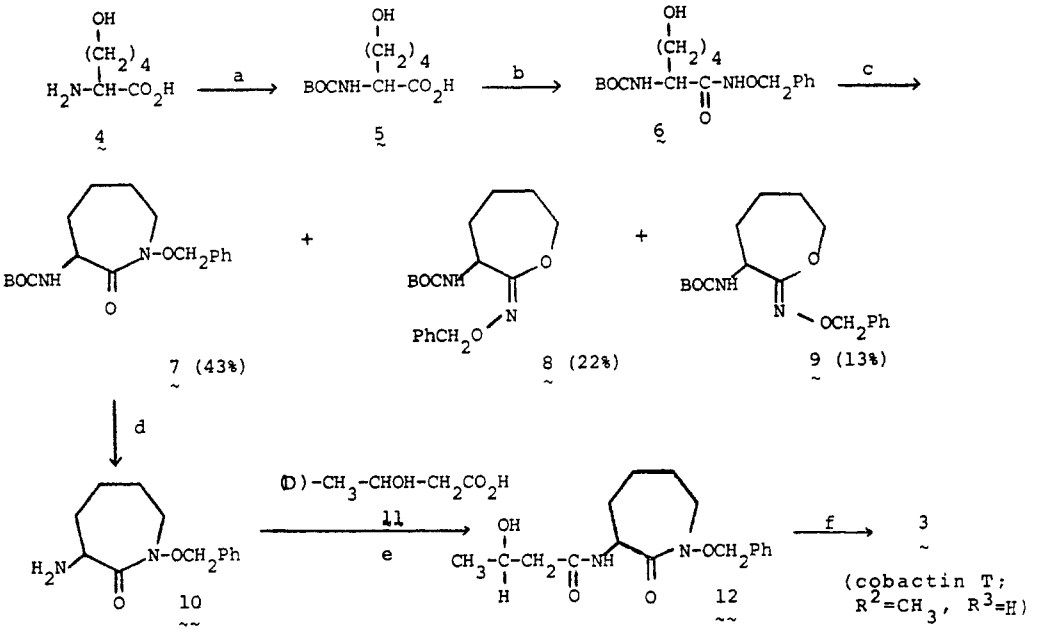
0022-3263/81/1946-2835$01.25/0

Scheme I[a]



[a] (a) Di-*tert*-butyl dicarbonate, (b) H_2NOCH_2Ph/carbodiimide, (c) DEAD/PPh_3, (d) CF_3CO_2H, (e) EEDQ, (f) H_2/Pd-C.

obtained by chromatography on silica gel by eluting with CH_2Cl_2/*i*-PrOH (99.5:0.5). Compounds **7** and **9** were separated by chromatography on silica gel by eluting with hexanes/ethyl acetate (80:20). The products of the cyclization reaction, **7–9**, were distinguished by the chemical shift of the multiplet for the ϵ-methylene proton in the NMR spectra. On the basis of the results of Johnson,[12] this peak should have the lowest δ value for the hydroxamate **7**, an intermediate value for the (*E*)-hydroximate **8**, and the highest value for the (*Z*)-hydroximate **9**. The three products exhibited peaks centered at δ 3.5, 4.25, and 4.5, respectively. The one with the δ 3.5 peak was assigned as the desired product **7**. This assignment was confirmed by application of the $FeCl_3$ test for hydroxamates to the reductively debenzylated compounds. Only the product assigned as the hydroxamate gave a positive result. This product, **7**, was isolated in 43% yield: mp 102.5–103.5 °C; $[\alpha]^{23}_D$ −11.3 ± 2.4° (*c* 2.2, MeOH); NMR ($CDCl_3$, Me_4Si) δ 1.6 (m, 15 H, includes *t*-Bu singlet at δ 1.48), 3.5 (br t, 2 H), 4.2 (m, 1 H), 5.0 (d, 2 H), 5.8 (br m, 1 H), 7.4 (s, 5 H). The racemic compound was prepared in our initial studies; mp 115–116 °C. The cyclic hydroximates **8** and **9** were isolated in 22% and 13% yields and had melting points of 84.5–85.5 and 94.5–95.5 °C, respectively. The ^1H NMR spectra of the three products differed mainly in the chemical shift of the ϵ-methylene protons as described above.[13]

The cyclic hydroxamate **7** was α-N deprotected with CF_3CO_2H and converted to the free base **10** in quantitative yield. No attempt was made to crystallize this oily amine; however, the NMR was consistent: δ 1.6 (br m, 6 H), 2.36 (br s, 2 H), 3.5 (br m, 3 H) 4.96 (s, 2 H), 7.4 (s, 5 H). D-β-Hydroxybutyric acid (**11**) was prepared by enzymatic reduction of lithium acetoacetate[14] with β-hydroxybutyrate dehydrogenase in the presence of NAD^+, (+)-galactose dehydrogenase, and (+)-galactose.[15] Coupling of **10** and **11** was achieved with a slight excess of 1-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline (EEDQ) in THF at 50 °C (12–22 h). Removal of THF and recrystallization of the residue gave *O*-benzylcobactin T (**12**) in 80% yield from **7**: mp 130.5–131.5 °C; $[\alpha]^{23}_D$ −16.3 ± 1.2° (*c* 5.5, CH_3OH).

The final deprotection was accomplished by hydrogenation of **12** (1 atm of H_2/Pd–C in CH_3OH). The product was recrystallized from acetone/ether to yield cobactin T (**3**): 79% (17% overall yield from L-ϵ-hydroxynorleucine (**4**)); mp 137–138.5 °C (lit.[2] mp 139.5 °C); $[\alpha]^{23}_D$ −90.5 ± 4° (*c* 1.5, H_2O) (lit.[2] $[\alpha]^{23}_D$ −88.9°).[16] Extensions directed toward the total synthesis of the mycobactins are being studied.

Acknowledgment. We are grateful to the National Institutes of Health (Grant GM 25845) and the Research Corp. for support of this research.

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(13) Interestingly, intermolecular PPh_3/DEAD-mediated alkylations of *O*-alkyl hydroxamates with α-N- and α-C-protected δ-*N*-hydroxynorleucine gave carbonyl oxygen alkylation (hydroximates) predominately. However, prior conversion of the hydroxyl group to a bromide followed by alkylation of sodium or potassium salts of the *O*-alkyl hydroxamates gave mainly *N*-alkyl products (4:1, N/O) as expected. Reaction of *N*-CBZ-*O*-benzylhydroxylamine ((CBZ)$NHOCH_2Ph$) directly with alcohols and PPh_3/DEAD gave N-alkylation exclusively. These observations necessitated a reevaluation of our previously reported model intermolecular alkylation studies.[9] It is now clear that while PPh_3/DEAD-mediated alkylation of (CBZ)$NHOCH_2Ph$ with alcohols gives complete N-alkylation and reaction with *O*-acyl hydroxamates, $RCONHOCOR^1$ provides typical mixtures of *N*- and *O*-alkyl products with *N*-alkyl products usually predominating; the alkylation of *O*-alkyl hydroxamates, $RCONHOR^1$, yields primarily the carbonyl-*O*-alkyl products (hydroximates).

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(16) All new crystalline compounds gave satisfactory elemental analyses (compounds **3**, **5**, **7–9**, and **12**).

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