When hexane solutions of II are refluxed for 5 h under a slow purge with N_2, II is converted quantitatively back into I.

Crystallographic Analyses. Crystals of I and II suitable for diffraction measurements were obtained as described above. The crystals were mounted in thin-walled glass capillaries. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated four-circle diffractometer using graphite monochromatized Mo K$\bar{\alpha}$ radiation. Unit cells were determined and refined from 25 randomly selected reflections obtained by using the CAD-4 automatic search, center, index, and least-squares routines.

For I the space group $P\bar{1}$ was assumed and confirmed by the successful solution and refinement of the structure. For II the space group $P2_1/n$ was established from the systematic absences observed in the data. Crystal data and data collections parameters are listed in Table V. All data processing was performed on a Digital Equipment Corp. PDP 11/45 computer with the Enraf-Nonius SDP program library (Version 16), or a VAX 11/750 with the VAXSDP purchased from B. A. Frenz and Assoc., College Station, TX. Absorption corrections of a Gaussian integration type were done for both structures. Neutral atom scattering factors were calculated by the standard procedures.[21a] Anomalous dispersion corrections were applied to all non-hydrogen atoms.[21b] Full-matrix least-squares refinements minimized the function $\sum_{hkl} w(|F_{obsd}| - |F_{calcd}|)^2$, where $w = 1/(\sigma(F)^2)$, $\sigma(F) = \sigma(F_{obsd}^2)/2F_{obsd}$ and $\sigma(F_{obsd}^2) = [\sigma(I_{raw})^2 + (PF_{obsd}^2)^2]^{1/2}/Lp$.

The structure of I was solved by a combination of Patterson and difference Fourier techniques. Only the osmium and sulfur atoms were refined anisotropically. Interatomic distances and angles with errors obtained from the inverse matrix obtained from the final cycle of least-squares refinement are listed in Tables I and II. Fractional atomic coordinates are listed in Table VI. Structure factor amplitudes are available.[22]

The structure of II was solved by a combination of direct methods and difference Fourier techniques. The four metal atoms were located in an electron-density map based on the phasing (MULTAN) of 160 reflections ($E_{min} \geq 2.10$). Only the osmium and sulfur atoms were refined anisotropically. Table III and IV list interatomic distances and angles with estimated standard deviations. Fractional atomic coordinates are listed in Table VII. Thermal parameters and structure factor amplitudes are available.[22]

Acknowledgment. We thank the National Science Foundation for support of this research through Grant CHE 80-19041, the Alfred P. Sloan Foundation for a fellowship to R.D.A., and Dr. Brian Johnson, University Chemistry Labs, Cambridge, for obtaining the mass spectra.

Registry No. I, 83928-36-3; II, 83928-37-4; $HOs_3(CO)_{10}(\mu\text{-}SC_6F_5)$, 83928-38-5; CO, 630-08-0.

Supplementary Material Available: Tables of structure factor amplitudes and thermal parameters are available for both structures (29 pages). Ordering information is given on any current masthead page.

(21) "International Tables for x-ray Crystallography"; Kynoch Press: Birmingham, England, 1975; Vol. IV. (a) Table 2.2B, p 99-101; (b) Table 2.3.1, p 149-150.

(22) See supplementary material.

Total Synthesis of a Mycobactin: Mycobactin S2

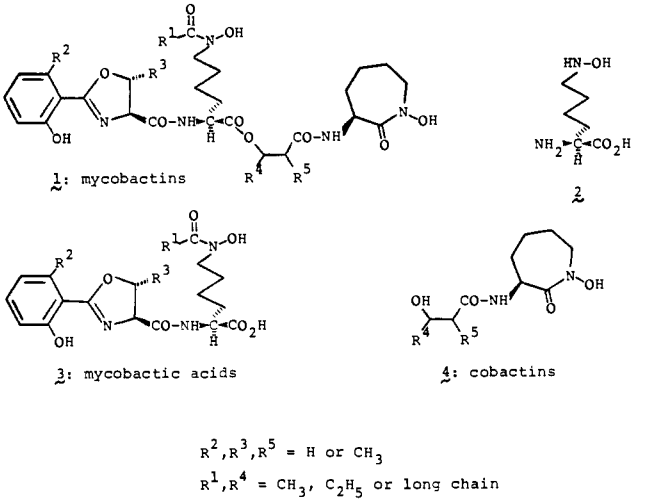
Peter J. Maurer and Marvin J. Miller*‡

Contribution from the Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556. *Received June 11, 1982*

Abstract: The synthesis of mycobactin S2, **1** (R^2, R^3, R^5 = H; R^1, R^4 = CH_3), is described. Mycobactin S2 is identical with natural mycobactin S except that the long hydrocarbon chain, R^1, is replaced by a methyl group. The synthesis was performed in a convergent manner by forming the ester linkage between the synthetic derivatives **13** and **28** of cobactin and mycobactic acid, respectively, followed by removal of the hydroxamate and phenol protecting groups. Compound **28** was obtained by saponification of the methyl ester, **27**, which was in turn prepared by dehydrative cyclization of the serine-containing dipeptide, **26**, with $SOCl_2$. Compound **26** was prepared by standard peptide coupling techniques from 2-(benzyloxy)benzoic acid, L-serine, and the previously reported **25**. Compound **13** was prepared by the dehydrative cyclization of α-*N*-Boc-L-ϵ-hydroxynorleucine *O*-benzylhydroxamate, **7**, to give **8**, followed by α-N deprotection and coupling with D-β-hydroxybutyric acid. Chirality was preserved throughout the synthesis giving a product with all S chiral centers, as in natural mycobactin S.

Microbial iron chelators or *siderophores* are important in the study of iron metabolism[1-3] and in the development of drugs for the treatment of iron-overloaded patients.[4-6] These compounds have evolved over millions of years for the purpose of sequestering iron(III) and enabling its transport through the outer membrane of the producing species.[7] The siderophores' high affinity and specificity for Fe(III) is due to the chemical nature of the chelating functional groups, which consist of either catecholate or hydroxamic acid residues.

The mycobactins, **1**, are perhaps the most structurally complex of the known siderophores. This family of compounds was characterized mainly by Snow and co-workers.[8] They demonstrated that all the mycobactins possess a nearly identical molecular nucleus with variations only in stereochemistry of the chiral centers and in the peripheral groups (R^1-R^5 in structure **1**). All the mycobactins form extremely stable hexadentate iron(III) complexes, by binding the iron with two hydroxamic acids and an 2-hydroxyphenyloxazoline residue. It is evident that these chelating moieties constitute the main challenge to a mycobactin synthesis. A mycobactin analogue lacking the three hydroxyl groups necessary for iron chelation was synthesized over a decade ago.[9] However, the first synthesis of a mycobactin containing



‡Fellow of the Alfred P. Sloan Foundation.

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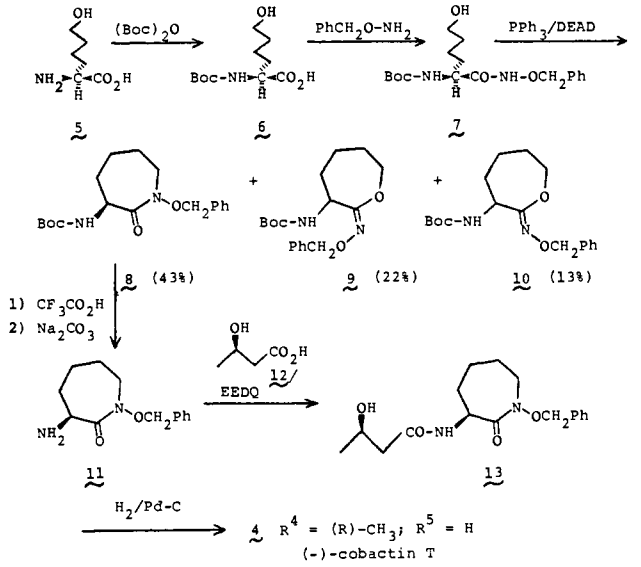
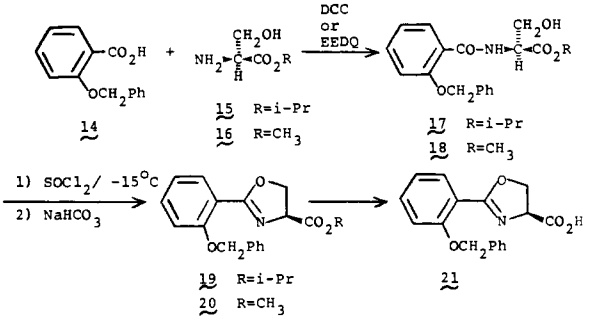
Scheme I



Scheme II



these groups has only recently been completed in our laboratories.

The two hydroxamate residues of the mycobactins are both derived from N^6-hydroxy-L-lysine, **2**. However, they differ in that one residue is acyclic whereas the other is present as a seven-membered *N*-hydroxylactam ring.

When a mycobactin is saponified, two fragments are obtained, a *mycobactic acid*, **3**, containing the acyclic N^6-hydroxylysine residue, and a *cobactin*, **4**, containing the cyclic residue.[8] We previously reported the synthesis of (−)-cobactin T, **4**, $R^4 = CH_3$, $R^5 = H$, in a communication,[10] and the synthesis of some acyclic N^6-acetyl-N^6-hydroxylysine derivatives in a paper describing the total synthesis of the hydroxamate siderophore, aerobactin.[11] This paper describes the synthetic details of the cobactin synthesis, the synthesis of the remaining mycobactin fragments in chiral form, and finally the assembly of the fragments into a mycobactin.

We have chosen for our initial synthetic target the simplified structure mycobactin S2 (**1**: R^1, $R^4 = CH_3$; R^2, R^3, $R^5 = H$).[12] While not a known natural product, this differs from natural mycobactin S only in that the heterogeneous long hydrocarbon chain (R^1 in **1**) is replaced by methyl.[13] All four chiral centers in this molecule are of the *S* configuration.

Results and Discussion

Synthesis of (−)-Cobactin T. Our synthesis of (−)-Cobactin T[10] is illustrated in Scheme I. After converting L-ε-hydroxynorleucine, **5**,[14,15] to the *N*-Boc compound, **6**,[10,11] the carboxyl group was converted to an *O*-benzyl hydroxamate, **7**, by coupling with *O*-benzylhydroxylamine. This coupling reaction was best carried out with 1-ethyl-3-(dimethylamino)propylcarbodiimide hydrochloride in aqueous solution at pH 4.5, although 2-ethoxy-*N*-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ) in THF also gave **7** in a lower yield. When **7** was treated with a slight excess of triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD), intramolecular alkylation took place leading to **8** (43% isolated yield) plus lesser amounts of the hydroximate side products, **9** and **10**. The products, **8–10**, were distinguished by the chemical shift of the ε-methylene protons in the ^1H NMR spectra[16] and confirmed by applying the $FeCl_3$ test for hydroxamic acids to the reductively debenzylated compounds (only **8** could give a positive result in this test).

The free amine, **11**, was obtained in quantitative yield by brief treatment of **8** with CF_3CO_2H followed by basification. D-β-Hydroxybutyric acid, **12**, was prepared by the enzymatic reduction of lithium acetoacetate[17] with a slight modification of the procedure of Passingham and Barton.[18] Compound **13** was obtained by coupling **11** and **12**, using a slight excess of EEDQ. Hydrogenation of **13** yielded (−)-cobactin T (**4**: $R^4 = CH_3$; $R^5 = H$) identical with cobactin T prepared by saponification of natural mycobactin T by melting point, optical rotation, and ^1H NMR spectra.

Synthesis and Attempted Coupling of the Mycobactin Oxazoline Fragment. Our original synthetic strategy for the total synthesis of a mycobactin included the preparation of the oxazoline fragment, (*S*)-2-(2-(benzyloxy)phenyl)-2-oxazoline-4-carboxylic acid, **21**. A review of the literature[19–22] indicated that the most efficient and convenient method of forming the oxazoline ring would be by dehydrative cyclization of the corresponding β-hydroxyamide, **17** or **18** (Scheme II). Thus, 2-benzyloxybenzoic acid[23] was coupled with the isopropyl and methyl esters of L-serine,[19] **15** and **16**, using DCC or EEDQ. The oxazolines were formed by treating the hydroxy amides with $SOCl_2$ at −15–0 °C in ether or THF (for **19** and **20**, respectively). The ether-insoluble oxazoline hydrochlorides formed initially.[20,21] These could be filtered or centrifuged from the reaction mixture and washed before neutralizing, thus removing ether-soluble impurities.

The saponification of the oxazoline esters, **19** and **20**, was not without difficulty since the product acid, **21**·$2H_2O$, had different optical rotations and melting points depending of the conditions and the particular ester used. In general, higher optical rotations were obtained with the methyl ester, **20**, than the isopropyl ester, **19**. Apparently saponification and racemization are competitive processes,[20] and the methyl ester is cleaved at a faster rate than the isopropyl ester. The literature indicates that the methyl ester corresponding to **20** but lacking the benzyloxy group can be saponified with no racemization,[21] whereas the ethyl ester and presumably higher esters undergo partial racemization.[20] On this basis, and on the basis of our observations during the attempted coupling of **21** with chiral amines,[24] it is believed that optically

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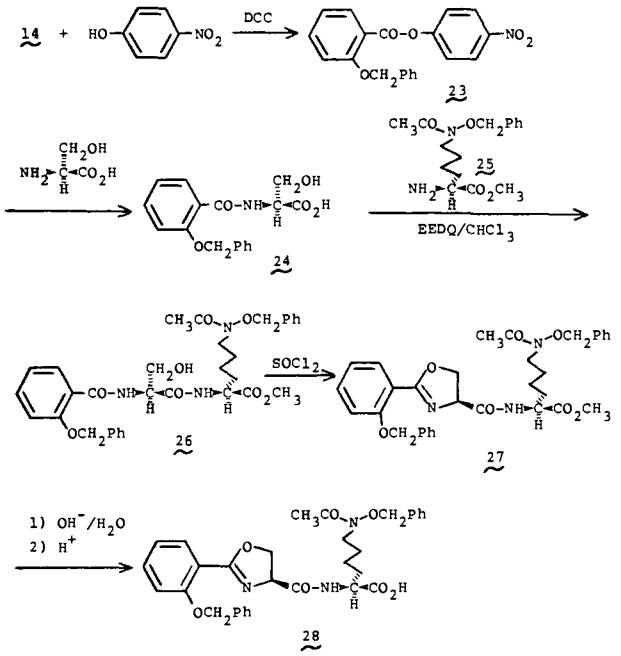
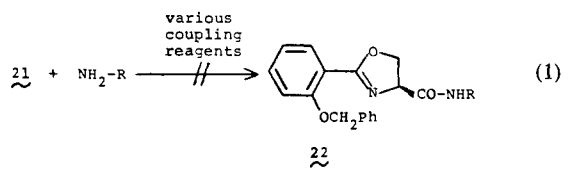
Scheme III



pure **21** was obtained from **20** but not from **19**. Elemental analysis indicates **21** is obtained as its *dihydrate*.

The coupling of **21** with model amines (benzylamine, glycine methyl ester, and N^6-Cbz-L-lysine methyl ester) was attempted many times with several different coupling reagents (isobutyl-chloroformate, DCC, DCC plus 1-hydroxybenzotrizole, water-soluble carbodiimides, *N*-ethyl-5-phenylisoxazolium-3′-sulfonate, EEDQ) but in no case could the desired amides, **22**, be obtained (see eq 1). This is in contrast to a report[9] describing the clean



(1)

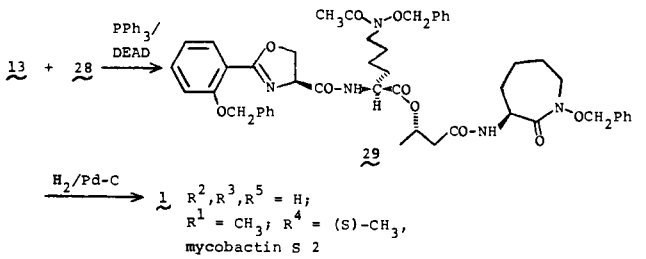
coupling of an acid, identical with **21** but lacking the benzyloxy group, with an amine. Full details of these attempts are described in a dissertation.[24]

Synthesis of Mycobactic Acid Derivatives. Since oxazoline acid, **21**, could not be coupled with amines, an alternative route to mycobactic acid derivatives was devised (Scheme III). Thus, instead of forming the oxazoline acid before coupling as originally suggested, the dipeptide, **26**, containing an acyclic serine residue, was assembled and subsequently cyclized to give the oxazoline peptide, **27**.

While partially racemic **24** could be obtained by saponification of ester **19**, the optically pure material was prepared by the reaction of L-serine with the 4-nitrophenyl ester, **23**. The amine, **25**, was prepared as a chloroform solution from the corresponding *N-tert*-butoxycarbonyl (*N*-Boc) protected compound as previously described.[11] Coupling of **24** and **25** using EEDQ in chloroform proceeded in high yield (92%) to give **26**. This yield was decreased, however, if EEDQ was used in greater than 5% excess. The oxazoline peptide, **27**, was formed as before, by treating with $SOCl_2$ at −15 °C, isolating the oxazoline hydrochloride and neutralizing. The acid, **28**, was then prepared by careful saponfication of **27**.

Compound **28** contains two chiral centers which might be susceptible to racemization under the reaction conditions used during its synthesis. Compounds **26–28** were also prepared with the partially racemic **24** described previously in order to determine whether diastereomers had in fact been formed. The limits of detection of the resulting diastereomers by ^1H NMR spectroscopy were about 5%, and none of the undesired diastereomers could

Scheme IV



be seen in the ^1H NMR spectra of compounds **26–28** prepared from optically pure **24**. Thus the route depicted in Scheme III appears to have proceeded to give the pure *S,S* diastereomers of products **26–28**.

Synthesis of Mycobactin S2. The final steps of our mycobactin synthesis consisted of forming an ester bond between acid **28** and alcohol **13** and subsequent removal of the three O-protecting benzyl groups (see Scheme IV). After several unsuccessful attempts at ester formation by carboxyl group activation using the reagent, *N,N*-bis[2-oxo-3-oxazolidinyl]phosphoramidic chloride,[25] we reasoned that carboxyl activation may not be viable since the moderately nucleophilic oxazoline nitrogen is disposed to attack the carboxyl via a six-membered ring. This would place a positive charge on the nitrogen, giving strong electrophilic character to the oxazoline ring which could then be destroyed by such weak nucleophiles as Cl^-.[21]

To avoid such problems, we decided to reverse the activation process by using the PPh_3/DEAD-mediated ester bond formation.[26] Since this reaction proceeds through a positively charged phosphonium salt derived from the alcohol and the carboxylate anion, it was expected that ion-pair formation would assist the ester-forming reaction and minimize interference from the nucleophilic oxazoline nitrogen. Indeed the PPh_3/DEAD-mediated ester bond formation proceeded as hoped, and protected mycobactin S2 (**29**) was isolated in 50% yield. Ample literature precedent[27] suggests that this process should result in inversion at the hydroxyl carbon. Thus, compound **29** formed in this way is of the *S,S,S,S* configuration and corresponds to mycobactin S.

Finally, mild hydrogenation of **29** provided a good yield of completely deprotected mycobactin S2, **1** (R^2, R^3, R^5 = H; R^1, R^4 = CH_3). The product was characterized by ^1H NMR spectroscopy and field desorption mass spectra. The UV spectrum was also essentially identical with mycobactin M which bears the same chromophore substituents. In addition, **29** had an apple green fluorescence under UV light, as do all the known natural mycobactins. When dissolved in $CHCl_3$ and layered with dilute aqueous $FeCl_3$, the $CHCl_3$ layer took on a characteristic red color, indicating that, as with the natural mycobactins, the ferric complex forms and distributes into the organic phase. As described in the Experimental Section, the preferential partition of the ferric complex into the organic phase of a CH_2Cl_2/H_2O mixture was also demonstrated by HPLC analysis. All of these properties support the structure of the synthetic mycobactin and demonstrate its similarity to the natural mycobactins.

On reverse-phase HPLC the synthetic mycobactin showed two peaks. However, one of these peaks was demonstrated to correspond to the ferric mycobactin complex which apparently forms in the loading loop of the instrument. The chromatogram indicates the absence of impurities detectable by UV monitoring of the eluants.

In conclusion, all of the basic functional components of the mycobactins have been synthesized in optically pure form and assembled into the first synthetic mycobactin (S2). Preliminary studies also indicate that even without a long lipophilic side chain

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the ferric mycobactins preferentially partition into organic phases.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were obtained on a Varian A60, EM 390, or XL 100, or a Nicolet NB 300 spectrometer in deuteriochloroform (unless otherwise stated) and are reported in parts per million downfield of internal tetramethylsilane (Me_4Si) i.e., δ units. HPLC analyses were performed with a Beckman Model 332 system with an Alltech RP 8 (reverse phase) analytical column. Thin-layer chromatography was performed on precoated sheets of EM silica gel 60 F-254. Optical rotations were measured with a Rudolf and Sons polarimeter, No. 574. Mass spectra were obtained by John L. Occolwitz (Eli Lilly Co.) using field desorption techniques. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN, or by M-H-W Laboratories, Phoenix, AZ.

L-*N*-Boc-ε-hydroxynorleucine Benzylhydroxamate, 7. (A) With EEDQ: *O*-benzylhydroxylamine hydrochloride (0.775 g; 4.86 mmol) and Et_3N (0.677 mL; 4.86 mmol) were placed in THF/EtOH (4:1; 40 mL) and refluxed to solution. After cooling, L-*N*-Boc-ε-hydroxynorleucine, **6**[11] (1.00 g; 4.05 mmol), was added followed by EEDQ (1.275 g; 5 mmol). The solution was stirred at 45 °C for 24 h, cooled, and evaporated. Ether (75 mL) was added and Et_3N·HCl was filtered off. The solution was washed twice with 0.2 M citric acid and once with 5% $NaHCO_3$. Then it was extracted with three portions of 0.4 N NaOH. The NaOH was washed once with ether, acidified to pH 6.7 (citric acid), and extracted twice with CH_2Cl_2. The CH_2Cl_2 was dried and evaporated to leave the product as an oil; 0.85 g, 60%. TLC indicated at least one contaminant. ^1H NMR (see below).

(B) With a water-soluble carbodiimide: L-*N*-Boc-ε-hydroxynorleucine, **6**[11] (1.00 g; 4.05 mmol), and *O*-benzylhydroxylamine hydrochloride (0.775 g; 4.86 mmol) were dissolved in H_2O (40 mL) by constant adjustment to pH 4.5 with 3 N NaOH. 1-Ethyl-3-(3-(dimethylamino)-propyl)carbodiimide hydrochloride (0.959 g; 5.0 mmol) in H_2O (3 mL) was added dropwise. After the mixture was stirred at room temperature for 15 min, a further 0.22 g of the carbodiimide was added. After a total of 30 min, the mixture was extracted with three portions of ether. This was extracted with three portions of 0.4 N NaOH, which was washed once with ether, acidified to pH 6.6 with citric acid, and extracted 3 times with CH_2Cl_2. This was dried and evaporated to leave the product as a colorless oil which slowly solidified: 1.137 g (80%); $[\alpha]^{23}_D$ −31.2 ± 1.7° (*c* 11, MeOH); ^1H NMR δ 1.4 (m, 15 H), 2.9 (s, 1 H), 3.5 (t, 2 H), 4.1 (m, 1 H), 4.9 (s, 2 H), 5.6 (d, 1 H), 7.4 (s, 5 H), 9.9 (s, 1 H); TLC one spot.

Also D,L-**7** was prepared by the water-soluble carbodiimide method from D,L-*N*-Boc-ε-hydroxynorleucine. NMR spectra and TLC properties were identical.

L-N^{α}-Boc-α-amino-*N*-(benzyloxy)caprolactam, 8. Compound **7** (1.137 g; 3.23 mmol) and PPh_3 (1.062 g; 4.04 mmol) were dissolved in dry THF (25 mL) and treated with DEAD (0.669 mL; 4.04 mmol). The solution was stirred at room temperature for 2 h The solvent was removed, and the residue was chromatographed on silica gel (2 × 40 cm) eluting with CH_2Cl_2/*i*-PrOH (99.5:0.5) to give pure **9** and a mixture of **8** and **10**. The latter mixture was separated by chromatography on silica gel (2 × 40 cm) eluting with ethyl acetate/hexanes (1:4). The three products were each crystallized from hexanes.

Compound **8** (464 mg; 43%): mp 102.5–103.5 °C; $[\alpha]^{23}_D$ −11.3 ± 2.4° (*c* 2.2, MeOH); ^1H NMR δ 1.6 (m, 15 H, includes *tert*-butyl singlet at 1.48), 2.5 (t, 2 H), 4.2 (m, 1 H), 5.0 (d, 2 H), 5.8 (br m, 1 H), 7.4 (s, 5 H).

Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.77; H, 8.15; N, 8.60.

Compound **9** (238 mg; 22%): mp 84.5–85.5 °C; ^1H NMR δ 1.48 (s, 9 H), 1.7 (br m, 6 H), 4.27 (m, 3 H), 5.01 (s, 2 H), 5.59 (d, 1 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.72; H, 7.68; N, 8.39.

Compound **10** (141 mg; 13%): mp 94.5–95.5 °C; ^1H NMR δ 1.0–1.9 (m, 15 H, includes *tert*-butyl singlet at 1.47), 4.15 (m, 1 H), 4.49 (t, 2 H), 4.87 (s, 2 H), 5.03 (d, 1 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.71; H, 7.72; N, 8.38.

Racemic **8** was prepared in initial studies; mp 115–116 °C, NMR spectrum identical with the L compound.

L-α-Amino-*N*-(benzyloxy)caprolactam, 11. Compound **8** (0.499 g; 1.45 mmol) was stirred at room temperature for 5 min with CF_3CO_2H (1 mL). Excess CF_3CO_2H was removed at reduced pressure and the residue was distributed between CH_2Cl_2 and dilute NH_4OH. The NH_4OH was extracted with two more portions of CH_2Cl_2. The extracts were combined, dried (K_2CO_3), evaporated, and vacuum desiccated to leave an oil: 0.349 g (100%); ^1H NMR δ 1.0–2.0 (m, 6 H), 2.84 (s, 2 H, NH_2), 3.52 (m, 3 H), 4.97 (s, 2 H), 7.39 (s, 5 H).

D-β-Hydroxybutyric Acid, 12. This was prepared by the method of Passingham and Barton,[18] with the modification of keeping the enzymes in small dialysis bags suspended in the reaction mixture. In this way several batches of substrate could be converted sequentially with the same enzymes. The free acid was obtained by continuous extraction of the acidified reaction mixture with ether. Removal of the ether and vacuum desiccation gave an oil: $[\alpha]^{22}_D$ −24.3 ± 0.7° (*c* 6, H_2O) [lit.[28] $[\alpha]^{22}_D$ −24.8°]; ^1H NMR (60 MHz, acetone-d_6) δ 1.22 (d, 3 H), 2.45 (d, 2 H), 4.16 (m, 1 H, 7.29 (br s, 2 H, OH/COOH).

Benzyl Cobactin T, 13. Compound **11** (0.342 g; 1.45 mmol) and D-β-hydroxybutyric acid, **12** (0.156 g; 1.5 mmol) were placed in dry THF (25 mL) and treated with EEDQ (0.455 g; 1.75 mmol). The mixture was stirred at 50 °C for 22 h. The solvent was removed and the residue was crystallized from ethyl acetate/ether to give 367 mg (79%) of white needles; mp 130.5–131.5 °C; $[\alpha]^{23}_D$ −16.35 ± 1.2° (*c* 5.5, MeOH); ^1H NMR δ 1.23 (d, 3 H), 1.3–2.2 (m, 6 H), 2.38 (m, 4 lines, 2 H), 3.52 (m, 2 H), 3.90 (s, 1 H, OH), 4.20 (m, 1 H), 4.49 (m, 1 H), 4.95 (m, 4 sym lines, 2 H), 7.10 (d, 1 H, NH), 7.40 (s, 5 H).

Anal. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.75. Found: C, 63.63; H, 7.44; N, 8.80.

(−)-Cobactin T, 4 (R^4 = (R)-CH_3; R^5 = H). Compound **13** (150 mg; 0.468 mmol) was dissolved in MeOH and treated with 10% Pd on carbon (10 mg). The mixture was stirred under 1 atm of H_2 overnight, filtered, and evaporated. The residue was crystallized from acetone/ether to give 85 mg (79%) of (−)-cobactin T: mp 137–138.5 °C (lit.[13] mp 139.5 °C); $[\alpha]^{23}_D$ −90.5 ± 4° (*c* 1.5, H_2O) (lit.[13] $[\alpha]^{23}_D$ −88.9°); ^1H NMR (acetone-d_6) δ 1.14 (d, 3 H), 1.2–2.1 (m, 6 H), 2.34 (m, 4 lines, 2 H), 2.84 (br s, 2 H, OH/NOH), 3.82 (m, 1 H), 4.08 (m, 1H), 4.57 (m, 1 H), 4.57 (m, 1 H), 7.45 (m, 1 H, NH).

Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.26; H, 7.87; N, 11.91.

2-(Benzyloxy)benzoic Acid, 14. This was prepared by the method of Farkas et al.[23] with slight modification. During the saponification of the intermediate benzyl ester, most of the solvent MeOH was allowed to distill out of the mixture during the last 30 min. Workup according to the original procedure gave an 85% yield with mp 74.5–75.5 °C (lit.[23] 48% yield; mp 76–78 °C).

L-Serine Isopropyl Ester HCl, 15, and L-Serine Methyl Ester HCl, 16. These were prepared by the procedure of Black et al.[19] by treating L-serine in the appropriate alcohol with dry HCl gas.

L-*N*-(2-(Benzyloxy)benzoyl)serine Isopropyl Ester, 17. 2-(Benzyloxy)benzoic acid (10.93 g; 0.048 mol) and L-serine isopropyl ester hydrochloride (8.8 g; 0.048 mol) were placed in CH_2Cl_2 (250 mL) and cooled on ice. Et_3N (6.66 mL; 0.048 mol) was added followed by DCC (12.38 g; 0.06 mol). The solution was stirred at 0 °C for 1 h and then at room temperature for 3 h. The mixture was concentrated to 140 mL, chilled, and filtered. The filtrate was washed twice with 5% Na_2CO_3 and once with 0.5 N HCl. Excess DCC was destroyed by stirring with HOAc (0.5 mL) and H_2O (10 mL) for 20 min and then filtering. The solvent was dried ($MgSO_4$), chilled, and refiltered. Evaporation of solvent left 14.5 g (85%) of **17** as an oil: ^1H NMR δ 1.20 (d, 6 H), 3.08 (br s, 1 H, OH), 3.88 (br s, 2 H), 4.6–5.2 (m, 2 H), 6.8–7.6 (m, 8 H), 8.17 (m, 1 H), 8.8 (d, 1 H, NH). With more dilute solutions the singlet at 3.88 is resolved into a doublet.

L-*N*-(2-(benzyloxy)benzoyl)serine Methyl Ester, 18. 2-(Benzyloxy)-benzoic acid (4.565 g; 0.020 mol) and L-serine methyl ester HCl (3.114 g; 0.020 mol) were placed in dry THF (100 mL) and treated with Et_3N (2.78 mL; 0.020 mol) followed by EEDQ (6.17 g; 0.025 mol). The mixture was stirred at 45 °C for 5 h, cooled, and filtered. The solvent was removed and the residue was crystallized from benzene to give 4.365 g (66%) of **18**: mp 128–129 °C; $[\alpha]^{26}_D$ +25.33 ± 1.5° (*c* 1.4, MeOH); ^1H NMR δ 2.46 (t, 1 H, OH), 3.67 (s, 3 H), 3.87 (m, 2 H), 4.81 (m, 1 H), 5.23 (s, 2 H), 6.9–7.6 (m, 8 H), 8.1–8.3 (m, 1 H), 8.78 (d, 1 H, NH).

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.59; H, 5.88; N, 4.30.

(*S*)-Isopropyl 2-(2-(Benzyloxy)phenyl)-2-oxazoline-4-carboxylate, 19. Compound **17** (9.15 g; 25.6 mmol) was dissolved in ether (150 mL) and chilled on ice. $SOCl_2$ (5.5 mL) was added such that the temperature remained below 5 °C. After stirring at 0 °C for 100 min, more $SOCl_2$ (3.0 mL) was added. Two more portions of $SOCl_2$ (each 3 mL) were added in 100-min intervals. Then the reaction mixture was left at −20 °C overnight. The resulting crystals were collected by centrifugation at 4 °C and washed by suspending in ice-cold ether and recentrifuging. The supernatant was returned to the freezer. The crystals were distributed between 10% Na_2CO_3 and ether. The ether layer was washed with 10%

(28) McCann, W. P.; Greville, G. D. *Biochem. Prep.* **1962**, *9*, 63.

Na_2CO_3, dried ($MgSO_4$), and evaporated to leave 4.812 g of needles. A further 1.006 g of the oxazoline was obtained from the supernatant after 24 more hours at −20 °C, with the same workup as above. Total yield: 5.818 g (67%); mp (ether/hexanes) 61–62 °C; $[\alpha]^{26}_D$ +117.2 ± 2° (*c* 2.8, MeOH); ^{1}H NMR δ 1.3 (d, 6 H), 4.6 (m, 3 H), 5.0 (m, 1 H), 5.2 (s, 2 H), 6.8–7.2 (m, 2 H), 7.2–7.7 (m, 6 H), 7.7–8.0 (m, 1 H).

(*S*)-Methyl 2-(2-(Benzyloxy)phenyl)-2-oxazoline-4-carboxylate, 20. Compound **18** (3.963 g; 12.03 mmol) was dissolved in dry THF (50 mL) and chilled on an ice/salt bath. $SOCl_2$ (6.0 mL) in dry THF (20 mL) was added with stirring over 70 min. The reaction mixture was left at −20 °C overnight and then poured into stirred ether (300 mL) at −20 °C. The precipitate was immediately collected on a chilled filter and partitioned between CH_2Cl_2 and 1 M $NaHCO_3$ at 0 °C. The CH_2Cl_2 was dried ($MgSO_4$) and evaporated, and the residue was crystallized from CH_2Cl_2/ether to give 2.177 g (58%) of colorless platelets: mp 121.3–121.8 °C; $[\alpha]^{26}_D$ +106.6 ± 3.6° (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 3.83 (s, 3 H), 4.4–5.1 (m, 3 H), 5.20 (s, 2 H), 6.9–7.1 (m, 2 H), 7.2–7.6 (m, 6 H), 7.7–7.9 (m, 1 H).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51; N, 4.50. Found: C, 69.22; H, 5.80; N, 4.55.

(*S*)-2-(2-(Benzyloxy)phenyl)-2-oxazoline-4-carboxylic Acid, 21. General Procedure: The oxazoline ester (either **19** or **20**) was dissolved in a small amount of solvent (either MeOH or THF/H_2O, 1:1) so that the substrate concentration was 0.07 M and treated with 1 equiv of a 0.5 N NaOH solution. After stirring for 3 min at room temperature, the reaction mixture was distributed between 12 volumes each of H_2O and ether. The H_2O layer was filtered, acidified to pH 2.75 (6 N HCl), and allowed to crystallize at 4 °C. The yields were 90–99%. Compound **19** saponified in MeOH gave **21**: mp 120–121 °C; $[\alpha]^{25}_D$ +11.1 ± 1° (*c* 1.4, 10% Na_2CO_3). Compound **19** saponified in THF/H_2O gave **21**: mp 123–124 °C; $[\alpha]^{25}_D$ +31.6 ± 3° (*c* 2.1, 10% Na_2CO_3). Compound **20** saponified in THF/H_2O gave **21**: mp 126–127 °C; $[\alpha]^{25}_D$ +49.7 ± 1.6° (*c* 2.3, 10% Na_2CO_3).

^{1}H NMR (acetic acid-d_4) δ 4.5 (m, 1 H), 4.8 (m, 2 H), 5.23 (s, 2 H), 6.9–7.2 (m, 2 H), 7.2–7.7 (m, 6 H), 7.8–8.0 (m, 1 H).

Anal. Calcd for $C_{17}H_{15}NO_4 \cdot 2H_2O$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.28; H, 5.89; N, 4.25.

L-*N*-(2-(Benzyloxy)benzoyl)serine, 24. (A) By saponification of 17: Compound **17** (5.14 g; 14.4 mmol) was dissolved in MeOH (75 mL) and treated with 0.5 N NaOH (29 mL). The mixture was stirred overnight at room temperature. The MeOH was evaporated and replaced with H_2O (220 mL). The solution was filtered and then acidified with a saturated solution of citric acid to pH 2.7. Ethyl acetate (0.5 mL) was added to promote crystallization of the product which was filtered off after a few minutes. The crystals were washed with H_2O, ethanol, and finally ether, then vacuum desiccated to leave 3.60 g (79%); mp 148–160 °C. Recrystallization from ethyl acetate gave mp 166.5–167.5 °C. This product was not optically pure. ^{1}H NMR: same as below.

(B) 4-Nitrophenyl ester method: First **4-nitrophenyl 2-(benzyloxy)-benzoate, 23**, was prepared as follows. 2-Benzyloxybenzoic acid (2.628 g; 11.52 mmol) and 4-nitrophenol (1.763 g; 12.67 mmol) were dissolved in dry ethyl acetate (75 mL), cooled to 0 °C, and treated with DCC (2.614 g; 12.67 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 4 h. The solution was washed 4 times with 10% Na_2CO_3, dried, and evaporated. The residue was dissolved in hot ethanol and allowed to crystallize to give 2.152 g (53.5%) of **23**: mp 100–102 °C; ^{1}H NMR δ 5.25 (s, 2 H), 7.0–7.7 (m, 10 H), 8.0–8.2 (m, 1 H), 8.2–8.45 (d, 2 H).

Anal. Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found: C, 68.50; H, 4.25; N, 3.98.

Compound **23** (1.927 g; 5.516 mmol), L-serine (0.58 g; 5.516 mmol), and Et_3N (1.534 mL; 11.032 mmol) were stirred in H_2O (80 mL) plus THF (110 mL) at room temperature for 22 h. Most of the THF was removed at reduced pressure, and the pH was adjusted to 5.3 with 6 N HCl. This solution was washed 3 times with ether and then acidified further to pH 2.3. After the solution set for several minutes, the crystals were filtered off to give 1.163 g (67%) of pure L-**24**: mp 131.5–132 °C; $[\alpha]^{23}_D$ +24.1 ± 0.5° (*c* 4.7, MeOH); ^{1}H NMR (acetone-d_6) δ 3.95 (d, 2 H), 4.76 (m, 1 H), 5.38 (s, 2 H), 5.9 (br s, 2 H, OH/COOH), 6.9–7.7 (m, 8 H), 8.1–8.25 (m, 1 H), 8.83 (d, 1 H, NH).

Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.74; H, 5.44; N, 4.44. Found: C, 64.34; H, 5.09; N, 4.10.

Compound 26. L-N^6-acetyl-N^6-(benzyloxy)-N^2-Boc-lysine methyl ester[11] (0.796 g; 1.95 mmol) was stirred with CF_3CO_2H (1.6 mL) for 5 min and then excess CF_3CO_2H was removed at reduced pressure. The residue was distributed between $CHCl_3$ and 5% Na_2CO_3. The $CHCl_3$ layer containing **25** was separated, dried briefly over K_2CO_3, and filtered. Pure (*S*)-**24** (0.616 g; 1.95 mmol) was added to this solution, followed by EEDQ (0.514 g; 2.08 mmol). The mixture was stirred overnight at room temperature. The solvent was removed and replaced with ethyl acetate. This solution was washed once with H_2O, once with 5% Na_2CO_3, 3 times with 0.2 N HCl, once with saturated $NaHCO_3$, and finally with saturated NaCl. After drying, the solvent was removed to leave **26** as an oil weighing 1.081 g (92%), which was sufficiently pure for further use: $[\alpha]^{23}_D$ +26.0 ± 1.2° (*c* 2.4, MeOH); ^{1}H NMR δ 1.0–2.0 (m, 6 H), 2.03 (s, 3 H), 3.55 (t, 2 H), 3.69 (s, 3 H), 3.8–4.2 (m, 2 H), 4.3–4.6 (m, 2 H), 4.74 (s, 2 H), 4.7–4.9 (m, 1 H), 5.23 (s, 2 H), 6.8–7.2 (m, 2 H), 7.3–7.7 (m, 11 H), 8.15–8.3 (m, 1 H), 8.86 (d, 1 H, NH); mass spectrum, *m/e* 91 (100, $C_7H_7^+$), 606 (76, M + 1), 605 (41, M^+).

When this reaction was carried out with **24** which had been prepared by the saponification method and was not optically pure, the following additional singlets were observed in the NMR: δ 2.05, 3.64, 4.80, and 5.26. These arise from the *R,S* diastereomer of **26**.

Compound 27. Compound **26** (pure *S,S* diastereomer; 0.833 g; 1.375 mmol) was dissolved in dry THF (7 mL) and chilled on an ice/salt bath (−10 to −15 °C). $SOCl_2$ (0.70 mL) in dry THF (4 mL) was added dropwise over 30 min. The solution was then left overnight at −20 °C and poured into dry ether (150 mL) at −20 °C. The precipitate which formed was immediately collected on a chilled funnel and distributed between CH_2Cl_2 and 5% $NaHCO_3$. The organic layer was dried and evaporated to leave an oil weighing 0.70 g (87%). This was further purified by chromatography on silica gel, eluting with ethyl acetate/CH_2Cl_2 (1:1): ^{1}H NMR δ 1.0–1.9 (m, 6 H), 1.99 (s, 3 H), 3.50 (t, 2 H), 3.72 (s, 3 H), 4.3–5.1 (m, includes 2 H singlet at 4.73, total 6 H), 5.23 (s, 2 H), 6.9–7.2 (m, 2 H), 7.3–7.65 (m, 11 H), 7.8–7.95 (m, 1 H); mass spectrum, *m/e* 587 (100, M^+), 91 (73, $C_7H_7^+$), 588 (25, M + 1).

Anal. Calcd for $C_{33}H_{37}N_3O_7 \cdot 0.5H_2O$: C, 66.42; H, 6.41; N, 7.04. Found: C, 66.54; H, 6.35; N, 7.15.

When the starting material, **26**, was a mixture of *S,S* and *R,S* diastereomers, the product, **27**, was also obtained as a diastereomeric mixture as indicated by additional singlets in the ^{1}H NMR spectrum at δ 2.07, 3.64, 4.78, and 5.28.

Dibenzyl Mycobactin Acid T2, 28. Compound **27** (pure *S,S* diastereomer; 0.448 g; 0.762 mmol) was dissolved in THF (20 mL) and treated with NaOH (0.77 mmol in 15 mL of H_2O). This solution was stirred at room temperature for 2 h, and then most of the THF was removed at reduced pressure. H_2O (12 mL) was added and the solution was washed with ether. After the mixture was acidified to pH 2.5 (1.2 N HCl), the acid was extracted with three portions of ethyl acetate, dried and evaporated to leave **28** as a light tan glass: 0.392 g (90%); $[\alpha]^{23}_D$ +14.8 ± 2°; ^{1}H NMR (90 MHz) δ 0.9–2.1 (m, 6 H), 1.97 (s, 3 H), 3.50 (t, 2 H), 4.3–5.1 (m, includes 2 H singlet at 4.69, total 7 H), 5.22 (s, 2 H), 6.8–7.15 (m, 2 H), 7.2–7.6 (m, 11 H), 7.74–7.9 (m, 1 H), 10.97 (s, 1 H, COOH); ^{1}H NMR (300 MHz) δ 1.15–1.3 (m, 2 H), 1.45–1.6 (m, 3 H), 1.7–1.85 (m, 1 H), 1.97 (s, 3 H), 3.50 (t, 2 H), 4.4–4.8 (m, includes 2 H singlet at 4.70, total 6 H), 4.9–5.0 (m, 1 H), 5.23 (s, 2 H), 6.9–7.0 (m, 2 H), 7.2–7.5 (m, 11 H), 7.75–7.8 (m, 1 H), 9.7 (s, b, 1 H, COOH); mass spectrum, *m/e* 574 (100, M + 1).

Anal. Calcd for $C_{32}H_{35}N_3O_7 \cdot 0.5H_2O$: C, 65.96; H, 6.23; N, 7.21. Found: C, 65.91; H, 6.29; N, 7.02.

When the starting material, **27**, was a mixture of *S,S* and *R,S* diastereomers, the product, **28**, was also obtained as a diastereomeric mixtures as indicated by additional singlets in the 90-MHz ^{1}H NMR spectrum at δ 2.05, 4.77, and 5.16.

Tribenzyl Mycobactin S2, (*S,S,S,S*)-29. Compound **28** (pure *S,S* diastereomer; 62 mg; 0.108 mmol), **13** (35 mg; 0.108 mmol), and PPh_3 (43 mg; 0.162 mmol) were placed in a flask, sealed with a septum, and flushed with N_2. Dry THF (1 mL) was added by syringe. When all the material had dissolved, DEAD (26 μL; 0.162 mmol) was added by syringe, with stirring. After stirring for 2 h at room temperature, the reaction mixture was separated by preparative TLC (silica gel; 0.2 × 20 × 20 cm) developing with ethyl acetate; R_f 0.21. Preparative TLC was repeated under the same conditions to obtain a highly pure product. This gave pure tribenzyl mycobactin S2 as an oil: 47.35 mg (50.1%); ^{1}H NMR (100 MHz) δ 1.33 (d, 3 H), 1.33–1.98 (m, 12 H), 1.99 (s, 3 H), 2.48 (m, 2 H), 3.50 (m, 4 H), 4.25–5.45 (m, includes two 2 H singlets at 4.71 and 5.22 and one 2 H doublet at 4.92, total 14 H), 6.8–7.6 (m, 18 H), 7.74–7.88 (m, 1 H); mass spectrum, *m/e* 876 (100, M + 1), 91 (68, $C_7H_7^+$), 875 (36, M^+); TLC (silica gel, CH_2Cl_2/*i*-PrOH 4:1 or ethyl acetate, one spot).

Mycobactin S2, 1 (R^2, R^3, R^5 = H; R^1 = CH_3; R^4 = (*S*)-CH_3). Tribenzyl mycobactin S2, **29** (47 mg; 0.054 mmol), was dissolved in *i*-PrOH (3 mL), treated with 10% Pd-C (25 mg), and stirred under H_2 (1 atm) at room temperature for 6 h. The mixture was filtered and evaporated to leave mycobactin S2 as an off-white powder: 29 mg (90%); ^{1}H NMR (100 MHz)[29] δ 1.1–2.0 (m, includes 3 H doublet at 1.36, total 15 H), 2.07 (s, 3 H), 2.47 (m, 2 H), 3.58 (t, 2 H), 3.73 (t, unsym, 2 H),

(29) For the NMR spectrum of authentic mycobactin S, see: Greatbanks, D., Bedford, G. R. *Biochem. J.* **1969**, *115*, 1047.

4.1-5.5 (m, 8 H), 6.8-7.2 (m, 2 H), 7.3-7.56 (m, 1 H), 7.6-7.76 (m, 1 H); UV (nm) 304, 258 (inflection), 248, 242; mass spectrum, *m/e* 606 (100 M + 1), 605 (44 M^+), 562 (13, M - CH_3CO), 648 (17, M + CH_3CO); fluorescence, apple green; forms red complex when treated with $FeCl_3$ which distributes into $CHCl_3$ in $CHCl_3/H_2O$ system.

HPLC analysis [Alltech 600 RP 8 column (25 cm × 0.25 in.) eluting with H_2O/MeOH (1:1) at 1.2 mL min^{-1} and detecting with a Beckman analytical optical unit at 254 nm]: two peaks with retention times 3.58 min and 4.56 min. Only the later peak was obtained when the mycobactin was first dissolved in CH_2Cl_2, shaken with dilute aqueous $FeCl_3$ to convert it to the ferric complex, and an aliquot of the CH_2Cl_2 layer subjected to HPLC analysis.

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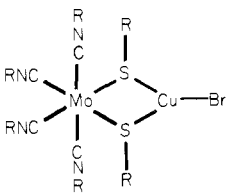
Synthesis and X-ray Structures of the Conformational Isomers of the Mixed Bimetal Complex $(t\text{-BuNC})_4Mo(\mu\text{-}t\text{-BuS})_2CuBr$

Nicholas C. Payne,[1a] Nobuyuki Okura,[1b] and Sei Otsuka*[1b]

Contribution from the Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, Japan 560. *Received March 17, 1982*

Abstract: The molecular fragment *cis*-$Mo(t\text{-BuS})_2$ has been found to act as a bidentate ligand, exhibiting affinity toward d^{10} metals. Reaction of $Mo(t\text{-BuS})_4$ or *cis*-$(Mo(t\text{-BuS})_2(t\text{-BuNC})_4$ with $CuBr(t\text{-BuNC})_3$ in acetone under dinitrogen gives crystals of formula $(t\text{-BuNC})_4Mo(\mu\text{-}t\text{-BuS})_2CuBr$. Two isomers have been isolated in the solid state, differing only in the relative arrangements of the *tert*-butyl substituents on the thiolato bridges. The anti-upright isomer **1** crystallizes from an acetone–toluene mixture with a molecule of diphenylacetylene in a monoclinic cell of dimensions a = 11.702 (2), b = 20.134 (4), and c = 10.455 (4) Å, β = 98.85 (2)°, Z = 2, and space group $P2_1$. Refinement by block-diagonal least-squares methods on F using 3690 unique, diffractometer data converged at R = 0.09. Compound **1** contains a MoS_2Cu core, with Mo–Cu = 2.628 (2) Å. The Mo atom has a distorted octahedral coordination geometry, with a large S–Mo–S angle of 105 (1)°. The Cu atom has almost ideal trigonal-planar geometry. A second isomer, **2**, may be crystallized from acetone in the orthorhombic space group *Pnma*, cell dimensions a = 21.994 (2), b = 16.411 (3), and c = 10.605 (1) Å, with Z = 4. Full-matrix least-squares refinement on F using 2882 averaged data converged at R = 0.08. *m* symmetry is imposed upon the molecule, which differs from **1** only in that the *t*-Bu substituents on the thiolato bridges adopt a syn-upright conformation. The interconversion of **1** and **2** has been demonstrated by variable-temperature ^1H NMR, and values of $\Delta G^{\ddagger}$ = 7.1 (7) kcal mol^{-1}, $\Delta H^{\ddagger}$ = 4.9 (2) kcal mol^{-1}, and $\Delta S^{\ddagger}$ = -6 (2) cal mol^{-1} deg^{-1} estimated for the conformational change.

Recently a number of bridged and unbridged molybdenum dimeric complexes have been prepared. Mixed-metal dinuclear compounds containing a molybdenum atom as one component, however, still remain a rarity.[2] The incentive for the present preparation of Mo–Cu complexes originated from the known antagonistic function of molybdenum ion against copper in ruminants.[3] Several types of Mo–Cu polymeric compounds have been prepared by Müller and his group, employing mainly MoS_4^{2-} as the source of the Mo component.[4] We have been interested in the interaction of thiolate ligand containing molybdenum species with Cu atoms. Since the reactive $Mo(t\text{-BuS})_4$[5] and other molybdenum 2-methyl-2-propanethiolate compounds[6] such as $Mo^{II}(t\text{-BuS})_2(t\text{-BuNC})_4$[7] were available, we have first examined interactions of these species with Cu(I) or Cu(II) ions. This study has led to the preparation of the novel title compound. Serendipitously we have isolated two conformational isomers in the solid state, differing only in the arrangements of the *t*-Bu substituents on the bridging thiolato ligands, namely anti-upright (**1**), and syn-upright (**2**). Their syntheses and single-crystal X-ray structure analyses are described herein.



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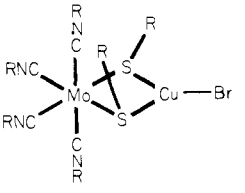

2

R = *t*-Bu

Experimental Section

Materials. $Mo(t\text{-BuS})_4$[5] and $Mo(t\text{-BuS})_2(t\text{-BuNC})_4$[7] were prepared according to the procedures described previously. All solvents were dried

(1) (a) On leave from Chemistry Department, University of Western Ontario, London, Ontario, N6A 5B7, Canada. (b) Osaka University.

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