diisopropylethylamine (11.4 mL, 65.4 mmol) in 80 mL of methylene chloride was added dropwise methoxyethoxymethyl chloride (7.47 ml, 65.4 mmol) under nitrogen. The resulting solution was allowed to warm to room temperature and stirred for 6 h. The completion of the reaction was indicated by TLC (ether, R_f(**2b**) 0.66; R_f(1) 0.65; clearly distinguished by sulfuric acid staining). After evaporation of the volatiles in vacuo, the residue was dissolved in ether, washed with saturated ammonium chloride (aq) and brine, and dried over magnesium sulfate. The dried solution was stirred with 2.5 g of silica gel for 2 min, the silica gel was removed by filtration, and concentration of the filtrate in vacuo afforded 11.25 g (93%) of **2b** as a colorless oil: IR (film) 1770 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.16; H, 7.30. Found: C, 51.93; H, 7.42.

2,3-*O*-(1-Methylethylidene)-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]ribonolactone (2c). A mixture of 1[18] (5.20 g, 27.6 mmol), imidazole (4.70 g, 69.1 mmol), and *tert*-butyldimethylsilyl chloride (5.00 g, 33.2 mmol) in 10 mL of dimethylformamide was stirred at room temperature under nitrogen for 22 h. The product was purified with three repetitive flash chromatographic separations using ether–petroleum ether 1:1 (R_f 0.78), 1:2 (R_f 0.67), 1:6 (R_f 0.25) sequentially to give 7.79 g (93%) of **2c** as white crystalls, mp 69–70 °C. IR (film): 1770 cm^{-1} (C=O). Anal. Calcd for $C_{14}H_{26}O_5Si$: C, 55.60; H, 8.67. Found: C, 55.83, H, 8.94.

1,4-Anhydro-2-deoxy-5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-D-*erythro*-pent-1-enitol (3c). Using the method of Ireland et al.,[8,9] a 1 M solution of diisobutylaluminum hydride in ether (30.1 mL, 30.1 mmol) was added dropwise over 15 min to a stirred solution of **2c** (7.00 g, 23.2 mmol) in 150 mL of ether at −78 °C under nitrogen. The reaction was quenched by addition of 6 mL of methanol after 2 h, and the mixture was allowed to warm to 0 °C. The mixture was then diluted with 75 mL of ether and extracted with disodium tartrate solution (0.5 M, aq). The resulting ether extract was dried over magnesium sulfate and evaporated in vacuo to yield 6.61 g (94%) of a colorless oil which was used in the next step without further purification.

To a solution of the above oil (6.54 g, 21.5 mmol) and carbon tetrachloride (2.49 mL, 25.8 mmol) in 60 mL of dry tetrahydrofuran, under nitrogen at −78 °C, was added 4.82 mL of 85% tris(dimethylamino)phosphine (22.5 mmol). After 30 min, the temperature of the reaction mixture was allowed to rise to 0 °C; the reaction mixture was then carefully added to a preprepared solution of lithium (1.79 g, 257 mmol) in 200 mL of ammonia kept at −78 °C. After ammonia refluxing (dry ice condenser) for 2 h, ammonium chloride (13.8 g, 258 mmol) was added. Ether (500 mL) was added to the resulting suspension, the ammonia was evaporated, and magnesium sulfate (5 g) was added. Filtration to remove salts and evaporation in vacuo afforded 10.8 of crude product which was purified by repetitive flash chromatography first with ether, then with 1:2 ether–petroleum ether to give 3.20 g (65%) of **3c** as a colorless oil. Anal. Calcd for $C_{11}H_{22}SiO_3$: C, 57.35; H, 9.62. Found: C, 57.40; H, 9.82.

1,4-Andro-2-deoxy-5-*O*-(methoxyethoxymethyl)-3-*O*-(trimethylsilyl)-D-*erythro*-pent-1-enitol (4d). To a precooled (ice bath) solution of **3b** (3.92 g, 19.2 mmol) in 150 mL of tetrahydrofuran under nitrogen were added triethylamine (8.1 mL, 57.6 mmol) in one portion and trimethylsilyl chloride (3.7 mL, 28.8 mmol) dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 1.5 h. After evaporation of the volatiles in vacuo, the residue was dissolved in ether, washed with saturated ammonium chloride (aq) and brine, and then dried over magnesium sulfate. The crude mixture was chromatographed on silica gel with ether–petroleum ether 1:3 (R_f 0.38) to afford 4.59 g (86%) of **4d** as a colorless oil: mass spectrum, m/z (relative intensity) 276 (0.1, $M^{+\cdot}$) 187 (62, M − $CH_2OCH_2CH_2OCH_3$), 157 (22). Anal. Calcd for $C_{12}H_{24}O_5Si$: C, 52.15; H, 8.75. Found: C, 52.88; H, 8.63.

1,4-Anhydro-2-deoxy-3-*O*-(methoxymethyl)-5-*O*-[tris(1-methylethyl)silyl]-D-*erythro*-pent-1-enitol (4g). To a precooled solution of **2d** (963 mg, 3.53 mmol) and diisopropylethylamine (98%, 2.51 mL, 14.1 mmol) in 7 mL of methylene chloride was added dropwise 1.07 mL of chloromethyl methyl ether (1.07 mL, 14.1 mmol). The resulting mixture was stirred for 42 h. After evaporation of the volatiles, purification was accomplished by flash chromatography (silica gel, 1:3 ether–petroleum ether, R_f 0.80) to afford 852 mg (76%) of **4g** as a colorless oil. Mass spectrum, m/z (relative intensity) 317 (0.01, M + 1^+), 273 (0.1, M − Me_2CH). Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: 60.77; H, 10.39.

1,4-Anhydro-2-deoxy-3,5-bis-*O*-[tris(1-methylethyl)silyl]-D-*erythro*-pent-1-enitol (4f). Compound **4f** was prepared from **3d** (1.00 g, 3.7 mmol) and triisopropylsilyl chloride (0.85 g, 4.4 mmol) by using a procedure similar to that described for the preparation of **2c**. The reaction mixture was allowed to stir overnight and then subjected to flash chromatography using 1:1 ether–petroleum ether for elution to afford 1.92 g of **4f** and triisopropylsilanol. Rechromatography of this material using 1:9 ether–petroleum ether (R_f 0.92) as eluant gave 1.45 g (92%) of **4f** as an oil. Anal. Calcd for $C_{23}H_{48}O_3Si$: C, 64.4; H, 11.3. Found: C, 64.2; H, 11.4.

1,4-Anhydro-2-deoxy-D-*erythro*-pent-1-enitol (5). To a stirred, ice-cooled solution of **3d** (1.00 g, 3.67 mmol) in 60 mL of tetrahydrofuran was added a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (3.86 mL, 3.86 mmol). The reaction was completed in 1 min based on TLC. After concentration in vacuo, the residue was chromatographed on silica gel with 2:1 ether–acetone (R_f 0.5) to afford 415 mg (98%) of **5** as an oil: mass spectrum, m/z (relative intensity) 116 (23, $M^{+\cdot}$); calcd for $C_5H_8O_3$ 116.0473, found 116.0479.

Acknowledgment. Financial support from the National Institute of General Medical Science (GM 30310), from Söderlundhs Minnesfond, and from Thuns fond is greatly appreciated.

Registry No. 1, 30725-00-9; **2a**, 72050-19-2; **2b**, 96760-89-3; **2c**, 75467-36-6; **2d**, 96760-90-6; **3a**, 72050-15-8; **3b**, 96760-91-7; **3c**, 96760-92-8; **3d**, 96760-93-9; **4a**, 86436-80-8; **4b**, 86436-81-9; **4c**, 96760-94-0; **4d**, 96760-95-1; **4e**, 96760-96-2; **4f**, 96760-97-3; **4g**, 96760-98-4; **4h**, 96760-99-5; **5**, 96761-00-1; **6a**, 96761-01-2; **6b**, 96761-02-3; methoxyethoxymethyl chloride, 3970-21-6; *tert*-butyldimethylsilyl chloride, 18162-48-6; trimethylsilyl chloride, 75-77-4; chloromethyl methyl ether, 107-30-2; triisopropylsilyl chloride, 13154-24-0.

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An Efficient Total Synthesis of Agrobactin and Its Gallium(III) Chelate

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A number of naturally occurring catecholamide iron chelators, siderophores, predicated on triamine backbones have recently been isolated and subsequently synthesized. These ligands include parabactin, isolated from *Paracoccus denitrificans*[1] and now accessible from two synthetic routes,[2,3] vibriobactin, isolated from *Vibreo cholera*[4] and recently synthesized,[5] and agrobactin, isolated from *Agrobacterium tumifaciens*[6] and as yet unavailable by synthetic methods. We now report the first synthesis of agrobactin utilizing the key intermediate ethyl 2,3-di-

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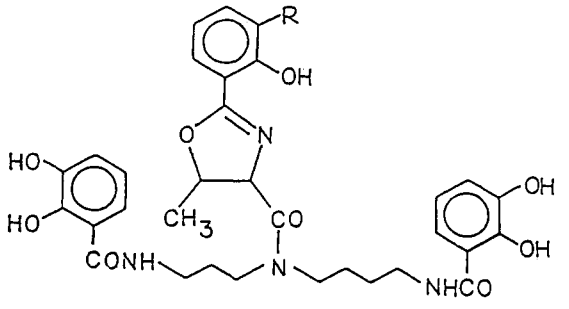
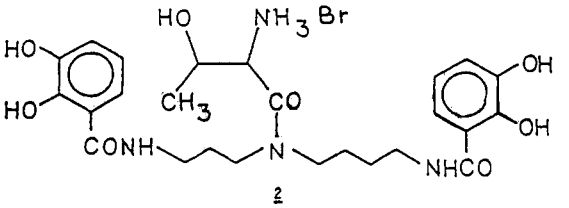
hydroxybenzimidate, the synthesis of which is also reported for the first time. This work complements our previous efficient synthesis of agrobactin A,[7] which results from hydrolytic opening of the oxazoline ring of agrobactin in acid.

The similarity of agrobactin (**1a**) to parabactin (**1b**) prompted us to utilize the methods we had developed in our laboratories for the synthesis of parabactin. Stereospecific formation of the acid-sensitive trans oxazoline ring was achieved in high yield by heating **2** with ethyl 2-hydroxybenzimidate, which was derived from 2-cyanophenol and ethanolic hydrogen chloride (Pinner reaction).[2] The condensation of **2** with dihydroxyimidate ester **3**, instead, would generate agrobactin. Unfortunately, 2,3-dihydroxybenzonitrile did not undergo addition of ethanol even upon heating in a high pressure reactor.



1a. R = OH, Agrobactin

1b. R = H, Parabactin



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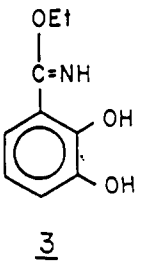
An alternate approach to the imidate ester was devised, based on O-alkylation of the amides.[8] It was necessary to prevent alkylation of the catechol hydroxyls of 2,3-dihydroxybenzamide. The benzyl protecting group was chosen because it can be removed catalytically under mild, neutral conditions.[9] In fact, Miller has accomplished selective O-benzyl hydrogenolysis (10% Pd–C) in the presence of a disubstituted oxazoline.[10]

Aminolysis of 2,3-dibenzyloxybenzoyl chloride (**4a**), available by a known route from 2,3-dihydroxybenzaldehyde,[11] furnished amide **4b** in 92% yield. Selective O-alkylation of **4b** with triethyloxonium hexafluorophosphate (1.1 equiv) in CH_2Cl_2, followed by basification,[8] provided protected imidate ester **5** in 81% yield.

Oxazoline-forming condensation of **5** with **2**, followed by debenzylation, would afford agrobactin (**1a**). However, we decided that catechol deprotection of **5** itself to the less hindered imidate **3** would allow a more convergent total synthesis of **1a**. Hydrogenolysis (10% Pd–C, 1 atm) of **5** to synthon **3** was performed in 73% yield. It is important



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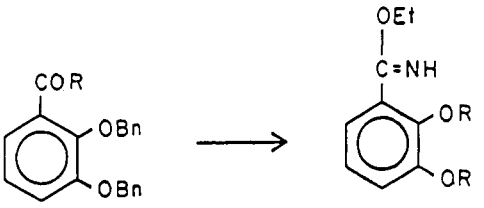

4a R = Cl

b R = NH_2

5 R = Bn

3 R = H

to note that benzyl cleavage was preferential to imidate reduction.

Finally, heating **2** with excess **3** in refluxing methanol and then purification on Sephadex LH-20 (20% ethanol–benzene) afforded agrobactin **1a** in 61% yield. The 300-MHz NMR spectrum was identical with that reported in the literature for naturally occurrng agrobactin. The duplication of signals for the α, β, and γ threonyl protons apparently arises from hindered rotation of the spermidine backbone about the N-4 amide bond.[9]

As a continuation of our program to evaluate siderophore–receptor interactions, the solution conformation of the gallium chelate of agrobactin was examined via 300-MHz ^1H NMR. The gallium chelate of agrobactin was prepared by adding a 10% excess of $Ga(NO_3)_3 \cdot 9H_2O$ to a degassed aqueous solution of **1a** at approximately pH 10, and then lowering the pH to about 7.4 and stirring 1 h, followed by lyophilization. The resulting white powder was further dried under vacuum in the presence of P_2O_5. The 300-MHz ^1H NMR spectrum of this gallium chelate in Me_2SO-d_6 very closely resembles the 300-MHz ^1H NMR spectrum of parabactin–gallium(III), which we recently reported.[12] On the basis of reasons analogous to the parabactin–gallium(III) chelate and CPK models, it is apparent that the trans-geometrical coordination isomers in the agrobactin gallium(III) chelate are precluded. However, owing to the unsymmetrical nature of the ligand, the chelating groups can form two different configurations about the gallium(III), namely the Λ and Δ optical isomers. The upfield shift of the γ-methyl signal from 1.5 to 0.5 ppm upon chelation, as was the case with parabactin, is consistent with exclusive formation of the Λ cis optical coordination isomer, in which the γ-methyl group lies in the shielding zone of an aromatic ring. However, in the CPK model of the Δ cis optical isomer of parabactin chelate, the γ-methyl group is not in the shielding zone of any aryl ring.[12] Moreover, an examination of the amide NH region of agrobactin–gallium(III) indicates that the complex forms exclusively the Λ cis-3,4 diastereomer.

The lack of a Λ cis-4,3 diastereomer was unexpected in view of its presence in the closely related parabactin–

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gallium chelate. A reexamination of the parabactin chelate using natural and our synthetic parabactin also indicated only two amide signals and one methyl signal. An exhaustive investigation of the previously prepared chelate suggested that the reported minor isomer was not the Λ cis-4,3 diastereomer but was in fact homoparabactin-gallium(III) chelate. Mass spectrometry of the parabactin sample used to make the parabactin-gallium(III) chelate utilized in our initial NMR study showed the molecular ions of the parabactin (*m/e* 620) and contaminating homoparabactin (*m/e* 634). After further examining the steps involved in the parabactin synthesis,[2] we determined that the problem arose from a sample of N^4-benzylspermidine contaminated with N^5-benzylhomospermidine. During the alkylation of *N*-(2-cyanoethyl)benzylamine with 4-chlorobutyronitrile,[13] small amounts of the symmetrical bisnitrile *N,N*-bis(3-cyanopropyl)benzylamine can be generated by reverse Michael reaction of acrylonitrile during the alkylation. Although small amounts of the contaminant could be carried through to the corresponding homospermidine, this higher boiling amine is normally separated by vacuum distillation. Alternatively, N^4-benzylspermidine can be prepared by using our recently reported polyamine reagents.[14] This efficient route precludes formation of the symmetrical contaminant and the associated separation problems.

In summary, agrobactin was prepared synthetically in a versatile high-yield synthesis, amenable to the generation of the nor- and homoagrobactin analogues. Furthermore, it appears from both parabactin- and agrobactin-gallium(III) chelates that the complexes exist exclusively as the Λ cis-3,4-isomer. This is an interesting finding since the free ligands have been shown to exist in solution in a number of different isomeric conformations arising from hindered rotation around the tertiary amide bond.

Experimental Section

All reagents, with the exception of gallium(III) nitrate nonahydrate (Alfa), were purchased from Aldrich Chemical Co. and were used without further purification. Sodium sulfate was employed as a drying agent. Melting points are uncorrected. Sephadex LH-20 was purchased from Pharmacia Fine Chemicals. Proton NMR spectra were recorded on a Varian T-60, EM-390, or a Nicolet NT-300 instrument, and unless otherwise noted, were run in $CDCl_3$ with chemical shifts given in parts per million downfield from an internal tetramethylsilane standard (coupling constants are in hertz). IR spectra were recorded on a Beckman Acculab 1 spectrophotometer. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA, or Galbraith Laboratories, Knoxville, TN.

2,3-Bis(benzyloxy)benzamide (4b). A solution of 2,3-bis(benzyloxy)benzoyl chloride (**4a**) (20.3 mmol)[11] in CH_2Cl_2 (80 mL) was added in portions to concentrated ammonium hydroxide (50 mL) and CH_2Cl_2 (30 mL) at 0 °C. After 1 day at room temperature, water (50 mL) was added, and the layers were separated. After two more extractions with CH_2Cl_2, the organic layer was washed with dilute $NaHCO_3$ and water and then dried and concentrated. Recrystallization with 50% aqueous ethanol afforded 6.19 g (92%) of **4b**, mp 130–132 °C: ^1H NMR δ 5.02 and 5.07 (2 s, 4 H), 6.0 (br, 2 H), 7.0–7.8 (m, 13 H); IR ($CHCl_3$) 3480 and 3360 (NH_2), 1670 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.75; H, 5.76, N, 4.19.

Ethyl 2,3-Bis(benzyloxy)benzimidate (5). To **4b** (6.99 g, 21.0 mmol) in CH_2Cl_2 (150 mL) was added triethyloxonium hexafluorophosphate (5.72 g, 23.1 mmol) and then more CH_2Cl_2 (50 mL). After stirring at least 1 day (room temperature, N_2), CH_2Cl_2 (50 mL) was added and the solution poured into ice-cold 1 M Na_2CO_3 (120 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), dried, and then concentrated. Recrystallization from hexane (55–60 °C) furnished 6.11 g (81%) of solid **5**, mp 42–43.5 °C: ^1H NMR δ 1.37 (t, 3 H, *J* = 7), 4.31 (q, 2 H, *J* = 7), 5.04 and 5.13 (2s, 4 H), 7.0–7.55 (m, 13 H), 8.58 (br s, 1 H); IR (neat) 3340 (NH) and 1640 (C=N) cm^{-1}.

Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.32; H, 6.45; N, 3.81.

Ethyl 2,3-Dihydroxybenzimidate (3). Into a solution of **5** (0.55 g, 1.52 mmol) in absolute, degassed ethanol (60 mL) was introduced 10% palladium on carbon (0.17 g), using acid-washed glassware. The suspension was stirred under a hydrogen atmosphere for 55 min. Hydrogen was removed at reduced pressure and replaced with argon. The suspension was heated to 80 °C and filtered under N_2 through a medium(10–15) frit, which was washed with hot ethanol (10–15 mL). Solvent removal gave 0.24 g of crude **3**, which was recrystallized from absolute ethanol to afford 0.200 g of **3** as light green needles in 73% yield, mp (sealed capillary) 193–195 °C dec: ^1H NMR (Me_2SO-d_6) δ 1.37 (t, 3 H, *J* = 7), 3.9–5.7 (br s and q, 5 H, *J* = 7), 6.3–7.2 (m, 3 H); IR (Nujol) 3100 and 1625 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.72; H, 6.15; N, 7.72.

Agrobactin (1a). Compounds **2** (0.128 g, 0.213 mmol) and **3** (0.17 g, 0.938 mmol, 4.4 equiv) were heated at reflux in dry, degassed methanol (20 mL) for 34 h. The cooled solution was dry packed onto LH-20 and eluted with 20% EtOH/benzene on an LH-20 column (22.4 g) to furnish 85 mg (61%) of **1a**. The NMR was identical with that reported for natural agrobactin.[9]

Anal. Calcd for $C_{32}H_{36}N_4O_{10}\cdot H_2O$: C, 58.71; H, 5.85; N, 8.56. Found: C, 58.85, H, 5.90; N, 8.54.

Acknowledgment. We wish to thank the National Institutes of Health for their generous support of this work (Grant No. AM 29936).

Registry No. **1a**, 70393-50-9; **2**, 82247-46-9; **3**, 96649-28-4; **4a**, 69146-58-3; **4b**, 96649-29-5; **5**, 96649-30-8.

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Titanium Tetrachloride Promoted Reactions of Allylic Trimethylsilanes and Oxetane

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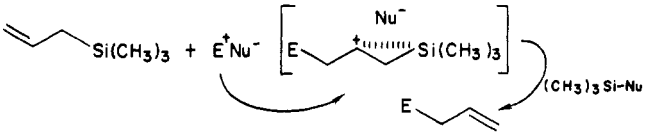
Many reactions of allylic trimethylsilanes involve electrophilic substitution with allylic rearrangement and loss of the trimethylsilyl group. These reactions may occur by addition of the electrophile to the carbon–carbon double bond to yield a carbocation intermediate which is stabilized by a β-trimethylsilyl group. Nucleophilic attack on silicon by an associated anion or solvent results in loss of the silyl group and formation of products.[1-3]



Epoxides react with Lewis acids to yield electrophiles that react regiospecifically with allylic trimethylsilanes to

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