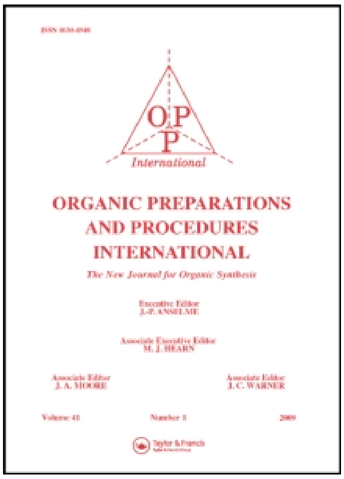

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A SYNTHESIS OF THE SIDEROPHORE 1,3,5-TRIS(N,N',N-2,3-DIHYDROXYBENZOYL)AMINOMETHYLBENZENE

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To cite this Article Schuda, Paul F. , Botti, Catherine M. and Venuti, Michael C.(1984) 'A SYNTHESIS OF THE SIDEROPHORE 1,3,5-TRIS(N,N',N-2,3-DIHYDROXYBENZOYL)AMINOMETHYLBENZENE', Organic Preparations and Procedures International, 16: 2, 119 — 125

To link to this Article: DOI: 10.1080/00304948409356174

URL: http://dx.doi.org/10.1080/00304948409356174

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A SYNTHESIS OF THE SIDEROPHORE

1,3,5-TRIS(N,N',N"-2,3-DIHYDROXYBENZOYL)AMINOMETHYLBENZENE

Submitted by Paul F. Schuda*+, Catherine M. Botti+ and Michael C. Venuti++
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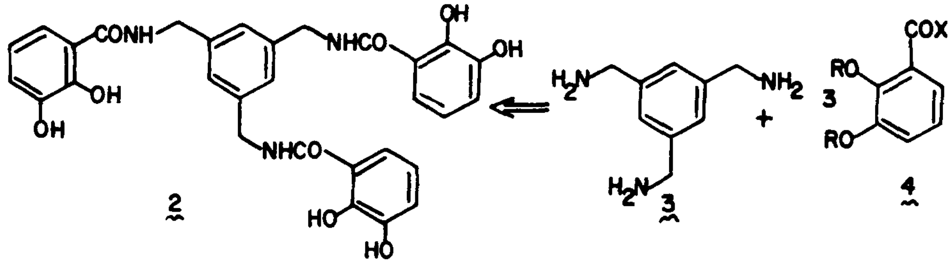
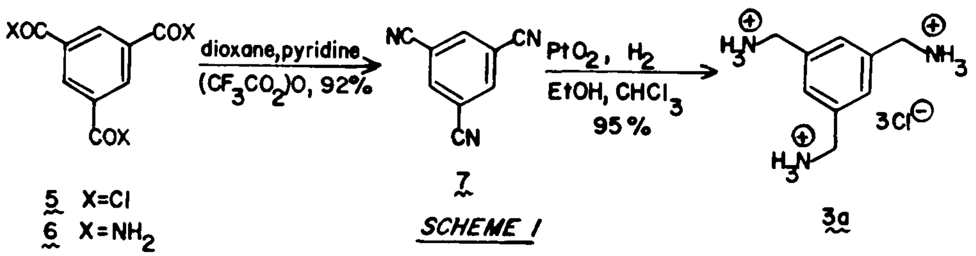
Enterobactin (1) is a potent iron chelator (K_f = 10^{52}). Although two routes[1,2] of the enterobactin mimic 2 have been reported, the difficulties encountered in scale-up and reproduction of one of the procedures and the

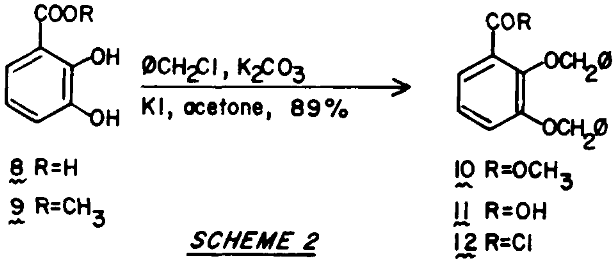


fact that experimental details for reference 2 are missing leads us to communicate our own results.

The dissection of 2 into triamine 3 and carboxylate 4 follows the retrosynthetic logic of the previous pathways.[1,2] The benzylic amine 3 (as 3a) and the 2,3-dihydroxybenzoyl portion were synthesized as shown in Schemes 1 and 2 respectively.

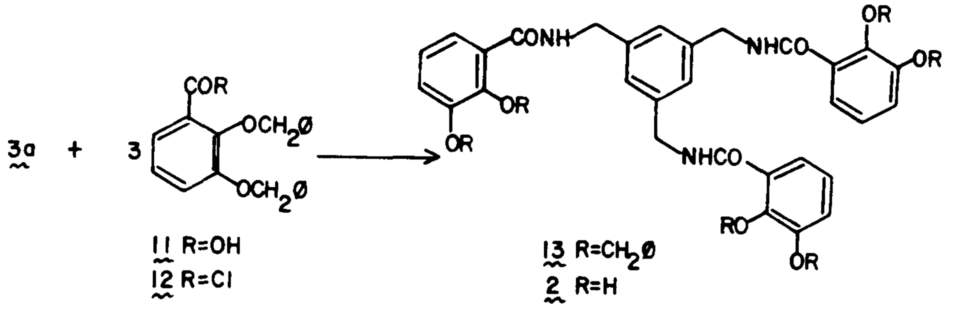


SCHEME 1



SCHEME 2

The desired coupling to 13 (Scheme 3) took place under Schotten-Bauman conditions,[3] and the benzyl ether protecting groups were subsequently removed by hydrogenolysis to afford 2. The mimic 2 of enterobactin (1) was



SCHEME 3

thus prepared in eight steps in 50% overall yield. This preparation is highly reproducible, easy to perform on a large scale, and only one chromatography is necessary in the sequence.

EXPERIMENTAL SECTION

1,3,5-Tricyanobenzene (7).- To a solution of 1,3,5-tricarboxamidobenzene (6)[1] (1.0 g, 0.005 mol) in dry pyridine (4.56 g, 0.058 mol) and dry dioxane (10 ml), cooled in an ice bath, was added dropwise trifluoroacetic anhydride (6.64 g, 0.032 mol) over a 45 min. period. After the addition was complete, the mixture was refluxed under N_2 for 45 hrs. The reaction was cooled and chloroform (30 ml) was added. The organic solution was washed with water and filtered through Celite to break up the emulsion. The organic layer was separated, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The residue was triturated with petroleum ether and then filtered to give a light yellow solid (690 mg, 92%). Recrystallization (CH_3OH) gave fine white crystals, mp. 251-253°, lit. (See reference 4). NMR ($CDCl_3$): δ 8.40 (s); IR (KBr): 3180, 2260 cm^{-1}; R_f = 0.81 (3:2 hexanes:ethyl acetate).

1,3,5-Tris(aminomethyl)benzene Trihydrochloride (3a).- A mixture of ethanol (166 ml) and chloroform (10 ml) was added to 1,3,5-tricyanobenzene (7) (1.00 g, 0.007 mmol) and PtO_2 (166 mg) and was stirred briefly until most of the solid went into solution. The resulting mixture was shaken under hydrogen (71 psig) for 48 hrs. The catalyst was removed by filtration and thoroughly washed with ethanol (ca. 100 ml). The combined filtrates were concentrated until approximately 30 ml of the solvent remained. Anhydrous ether (80 ml) was added and a voluminous white precipitate formed. The precipitate was filtered, washed rapidly with ca. 30 ml of anhydrous ether, and dried *in vacuo* to yield a white very hygroscopic solid 3a (1.69 g, 95%); NMR (D_2O), DSS: δ 4.50 (bs, 6H), 7.75 (s, 3H).

Methyl 2,3-Dihydroxybenzoate (9).- Boron trifluoride etherate (5 ml) was added to a solution of 2,3-dihydroxybenzoic acid (8) (6.78 g, 0.044 mol) in anhydrous methanol (100 ml). The mixture was heated at reflux for 24 hrs. After cooling to room temperature, the methanol was removed at 35° *in vacuo* and methylene chloride (100 ml) was added to the residue. The organic solution was washed with saturated sodium bicarbonate, dried over $MgSO_4$, filtered, and evaporated at 35° *in vacuo* to give a light brown solid (7.40 g, 100%). Recrystallization (hexanes:ether) yielded fine white crystals, mp. 80-81°, lit.[5] 76-79°; NMR ($CDCl_3$): δ 3.92 (s, 3H), 5.70 (brs, 1H), 6.50-7.35 (m, 3H), 10.75 (s, 1H). IR ($CHCl_3$): 3580, 3180, 3060, 1685 cm^{-1}; R_f = 0.47 (3:2 hexanes-ethyl acetate).

Methyl 2,3-Dibenzyloxybenzoate (10).- Methyl 2,3-dihydroxybenzoate (9) (9.86 g, 0.058 mol) was added to a mixture of benzyl chloride (16.44 g, 0.130 mol), potassium carbonate (56 g, 0.406 mol), potassium iodide (21.58 g, 0.130 mol) and acetone (400 ml). The solution was heated at reflux for 15 hrs, then cooled and filtered. The volatiles were evaporated under reduced pressure and ether (200 ml) was added to the residue. The organic layer was washed with water (2 x 70 ml), dried over $MgSO_4$, filtered, and evaporated at 35° *in vacuo* to yield a yellow solid. Petroleum ether (100 ml) was added, the mixture was cooled to 0° and triturated. The solid formed was filtered while cold and washed with a minimal amount of cold petroleum ether to yield a light yellow solid (18.07 g, 89%). Recrystallization (hexanes) yielded fine white crystals, mp. 60-61°, lit.[6] 62.5-63.5°; NMR ($CDCl_3$): δ 3.80 (s, 3H), 5.10 (s, 4H), 6.80-7.50 (m, 13H); IR ($CHCl_3$): 3010, 2980, 1730 cm^{-1}; R_f = 0.79 (3:2 hexanes-ethyl acetate).

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.92

Found: C, 75.76; H, 5.92

2,3-Dibenzyloxybenzoic Acid (11).- Methyl 2,3-dibenzyloxybenzoate (10)

(9.81 g, 0.028 mol) was added to a solution of sodium hydroxide (20 g) in water (150 ml) and dimethoxyethane (60 ml). The solution was heated at reflux for 14.5 hrs. The reaction was cooled and concentrated under reduced pressure until all the dimethoxyethane was evaporated. The solution was acidified with conc. HCl and a white precipitate formed. The mixture was cooled to 5° and filtered. The solid was washed with 30 ml of ice-cold water, and air-dried to afford 9.32 g (99%) of <u>11</u>. Recrystallization (hexanes:ethyl acetate) gave fine white crystals mp. 122-124°, lit.[7] 124°; NMR ($CDCl_3$): δ 5.02 (s, 2H), 5.10 (s, 2H), 7.00-7.60 (m, 13H), 10.60 (bs, 1H); IR ($CHCl_3$): 3010, 3000, 1750 cm^{-1}; R_f = 0.20 (3:2 hexanes:ethyl acetate).

<u>Anal</u>. Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43

Found: C, 75.11; H, 5.58

<u>2,3-Dibenzyloxybenzoyl Chloride (12)</u>.- Oxalyl chloride (1.88 g, 0.015 mol) was added to a flask containing dry benzene (20 ml) and 2,3-dibenzyloxybenzoic acid (<u>11</u>) (2.50 g, 0.007 mol). Upon addition of a drop of N,N-dimethylformamide, the reaction became mildly exothermic. The solution was stirred at room temperature under nitrogen for 12 hrs. The volatiles were removed under reduced pressure to yield a yellow liquid, which upon addition of low boiling petroleum ether and subsequent cooling to 0° crystallized to a beige solid (2.56 g, 100%). Recrystallization (hexanes) gave fine white crystals, mp. 55-56°, lit.[8] 55-56°; NMR ($CDCl_3$): δ 5.02 (s, 4H), 6.80-7.40 (m, 13H); IR ($CHCl_3$): 3100, 2950, 1790 cm^{-1} R_f = 0.55 (3:2 hexanes-ethyl acetate).

<u>1,3,5-Tris(N,N',N",-2,3-dibenzyloxybenzoyl)aminomethylbenzene (13)</u>.- A solution of 2,3-dibenzyloxybenzoyl chloride (<u>12</u>) (5.04 g, 0.014 mol) in tetrahydrofuran (30 ml) was added over a period of 2 hrs to a cold (0°), vigorously stirred mixture of 1,3,5-tris(aminomethyl)benzene trihydro-

chloride (3a) (1.10 g, 0.004 ml), and sodium hydroxide (1.20 g, 0.030 mol) in water (40 ml). After the addition was complete, the solution was stirred for an additional hour at room temperature. The tetrahydrofuran was evaporated under reduced pressure and water (30 ml) was added. The aqueous layer was extracted with ethyl acetate (2 x 60 ml). The organic layer was washed with 5% $NaHCO_3$ (20 ml), 5% HCl (20 ml), and saturated NaCl (20 ml). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield a crude solid. Chromatography on silica gel (100 g) and elution with 1:4 ethyl acetate-dichloromethane gave a white foam (3.35 g, 75%); NMR ($CDCl_3$): δ 4.24 (d, 6H, J = 6Hz), 4.48 (s, 6H), 5.00 (s, 6H), 6.70-7.65 (m, 42H), 8.00 (t, 3H, J = 6Hz); IR ($CHCl_3$): 3480, 3020, 1660 cm^{-1}; R_f = 0.20 (1:9 ethyl acetate:dichloromethane.

1,3,5-Tris(N,N',N"-2,3-dihydroxybenzoyl)aminomethylbenzene (2).- 1,3,5-Tris(N,N',N"-2,3-dibenzyloxybenzoyl)aminomethylbenzene (13) (1.20 g, 0.001 mol) in absolute ethanol (180 ml) was heated on a steam bath until it dissolved. Distilled acetic acid (8 ml) was added. The solution was added to 10% Pd/C (800 mg) and the resulting suspension was shaken under hydrogen (68 psig) for 48 hrs. The catalyst was removed by filtration and thoroughly washed with ethanol (ca. 100 ml). The solution was concentrated under reduced pressure and ethyl acetate (25 ml) added to the residue. The organic layer was washed with 5% HCl (20 ml) and saturated NaCl (20 ml), then dried with Na_2SO_4, filtered, and evaporated. Trituration with dichloromethane and filtration gave a light tan solid. The solid was heated at 80° under vacuum (0.1 mm of Hg) for 12 hrs to give 13 (570 mg, 93%) mp. 128-130°, lit.[2] 128-132°; NMR (d_6-acetone, 100MHz): δ 4.50 (br, s, 6H), 6.60 (t, 3H, J = 7Hz) 6.95 (dd, 3H, J = 2Hz, 7Hz), 7.25 (dd, 8H, J = 2Hz, 7Hz), 7.30 (s, 9H, [6H exh 20]), 8.70 (br, t, 3H); IR (KBr): 3380, 2950, 1640 cm^{-1}; R_f = 0.68 (acetone). The NMR of this compound (d_6-acetone) was identical to a sample provided by Dr. William Rastetter.

Acknowledgment.- We would like to thank the National Institutes of Health for their generous support of this research (AI 15750-03).

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