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Trishydroxamates and triscatecholates based on monosaccharides and *myo*-inositol as artificial siderophores

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Abstract

New trishydroxamates and triscatecholates based on methyl α-*D*-glucopyranoside, methyl α-*D*-galactopyranoside, methyl α-*D*-ribopyranoside and methyl α-*D*-xylopyranoside as well as on 1,3,5-tri-O-benzyl-*myo*-inositol were synthesized. *N*-Methylsuccinohydroxamate, *N*-methylglutarohydroxamate and their O-benzoyl derivatives were used as hydroxamate moieties. 2,3-Dihydroxybenzoyl derivatives and acylated compounds as well as 2,3- and 3,4-dihydroxybenzylidenehydrazino derivatives, partly with spacer groups, were utilized as catecholate components. The siderophore activity of the prepared siderophore analogues was examined by a growth promotion assay with various Gram-negative bacteria and mycobacteria and by the CAS-assay. Some trishydroxamates and triscatecholates showed siderophore activity on Gram-negative bacteria and triscatecholates on mycobacteria. Iron complexes of the trishydroxamates act as siderophores for all types of iron transport mutants. The recognition and uptake specificity of these compounds was studied by *E. coli* siderophore receptor and iron transport mutants. Structure activity correlations are discussed.

Introduction

Most of the bacterial siderophores contain hydroxamates or catecholates as chelating groups and amino acids or dipeptides as scaffolds (Drechsel *et al.* 1998). Many synthetic analogues of these compounds were synthesized to study structure-activity correlations and to identify new biological active compounds like chelators against iron overload diseases (Bergeron *et al.* 1999), siderophore components for iron transport-mediated uptake of antibiotics (Budzekiewicz 2001) and antimicrobial agents e.g. against *Plasmodium* species (Pradines *et al.* 1996). Preferrentially synthetic analogues of the triscatecholate enterobactin, and of the trishydroxamates ferrichrome and ferricrocin were published (Shanzer *et al.* 1996) (Figure 1). Cyclitols were used to substitute the unstable trilacton backbone of enterobactin (Coleman *et al.* 1992; Tse & Kishi 1993). We prepared enterobactin analogues containing a *myo* inositol scaffold (Schnabelrauch *et al.* 1998). Recently we published triscatecholate derivatives of methyl α-D-glucopyranoside as highly active siderophores in Gram-negative bacteria and mycobacteria (Heggemann *et al.* 2001). These compounds could form very stable iron complexes (Dhungana *et al.* 2001) and exhibited activity against *Plasmodium falciparum* (Rotheneder *et al.* 2002). Biscatecholates of diamino acids (Schnabelrauch *et al.* 2000), triscatecholates based on triamines (Heinisch *et al.* 2002a), and xenosiderophores like ferrichrome and other hydroxamates (Schumann & Möllmann 2001) can be active as siderophores and promote the growth of mycobacteria under iron depletion.

Here we report on the synthesis and siderophore activity of new trishydroxamates based on methyl α-D-glucopyranoside, methyl α-D-galactopyranoside, methyl α-*D*-ribopyranoside, methyl α-D-xylopyrano-

side, on 1,3,5-tri-O-benzyl-myo-inositol, on triscatecholates based on methyl α-D-glucopyranoside and methyl α-D-galactopyranoside and on dihydroxybenzylidenehydrazino derivatives based on methyl α-D-glucopyranoside. The siderophore activity of the new analogues and some of their iron complexes was examined by growth promotion assays with various Gram-negative bacteria and mycobacteria and by the CAS-assay.

Material and methods

Synthesis of the siderophore analogues

General: ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance DR 300 spectrometer, respectively. The chemical shifts δ are given in ppm related to tetramethyl silane as internal standard. The coupling constants J are reported in Hz. Here only ^{1}H-NMR spectra of few test substances were given as examples. ^{13}C NMR spectra and ^{1}H-NMR spectra of the other compounds confirming the structures were recorded and can be requested from the authors. Mass spectra were obtained by a Finnigan MAT 95 XV sector field mass spectrometer using electron-spray ionisation (ESI) technique. The measurements of the optical rotations were performed with a Kernchen Polarimeter PROPOL. Column chromatography was accomplished using silica gel (Merck 60, 0.040–0.063 mm or Merck 60, 0.60–0.120 mm). Purification of the compounds by preparative HPLC was performed on an ABIMED GILSON apparatus equipped with an 115 UV detector (254 nm) and a KNAUER VERTEX reversed phase column (250 × 32 mm or 50 × 20 mm) packed with Eurospher 100-C18 (7 μ). Acetonitrile and water were used as eluents, beginning with ratio 30:70 (v/v) and achieving 100:0 (v/v) after a period of 20 min (flux rate 10 or 20 ml min). Thin layer chromatography (TLC) was conducted with precoated silica plates (Merck 60 F254) applying UV detection. Solvents and reagents used were dried and purified by standard methods.

*Methyl 2,3,4-tris-O-[4-(N-benzoyloxy-N-methylcarbamoyl)-n-butyryl]-6-O-trityl-α-D-glucopyranoside (**6a**) $C_{65}H_{67}N_3O_{18}$* (1178.27)
Dicyclohexylcarbodiimide (950 mg, 4.53 mmol) was added at 0 °C to a solution of methyl 6-O-trityl-α-D-glucopyranoside (**1**) (500 mg, 1.16 mmol), N-benzoyloxy-N-methyl-glutaramide (1.2 g, 4.53 mmol) and N,N-dimethylaminopyridine (DMAP) (0.1 g) in dichloromethane (100 ml) with stirring. The reaction mixture was stirred for 1 h at 0 °C and for 24 h at ambient temperature. Then the precipitated dicyclohexylurea was filtered. The solution was acidified with 1 N HCl and evaporated. The residue was dissolved in ethyl acetate. The solution was washed with brine and water, dried over Na_2SO_4, filtered and evaporated. The raw product was purified by HPLC to obtain **6a** (700 mg, 0.59 mmol) as a colourless foam, yield 55%. $[\alpha]_D^{20}$ +52.4 (c 7.5 chloroform). ^{1}H-NMR ($CDCl_3$): 1.92–1.97 (m, 6H, CH_2), 2.19–2.38 (m, 12H, CH_2CO), 3.08 (d, J = 3.7, 2H, H6), 3.34 (s, 3H, αOCH_3), 3.37–3.40 (3s, 9H, NCH_3), 3.85 (dt, J = 3.8, 10.2, 1H, H5), 4.83 (dd, J = 3.7, 10.2, 1H, H2), 4.96 (d, J = 3.2, 1H, H1), 4.97 (t, J = 10.0, 1H, H4), 5.33 (t, J = 10.0, 1H, H3), 7.19–7.27 (m, 9H), 7.42–7.52 (m, 12H), 6.60–7.69 (m, 3H), 8.03–8.12 (m, 6H). MS (ESI) m/z 1200.9 $[M+Na]^+$.

*Methyl 2,3,4-tris-O-[3-(N-benzyloxy-N-methylcarbamoyl)-n-propionyl]-6-O-trityl-α-D-glucopyranoside (**6b**), $C_{62}H_{67}N_3O_{15}$* (1094.24)
The compound was prepared similar to **6a** from **1** and N-benzyloxy-N-methyl-succinamide as a colourless foam, yield 71%. $[\alpha]_D^{20}$ +49.5 (c 10.0, chloroform). MS (ESI) m/z 1112.0 $[M+NH_4]^+$, 1117.0 $[M+Na]^+$.

*Methyl 2,3,4-tris-O-[4-(N-benzyloxy-N-methylcarbamoyl)-n-butyryl]-6-O-trityl-α-D-glucopyranoside (**6c**) $C_{65}H_{73}N_3O_{15}$* (1136.32)
The compound was prepared similar to **6a** from **1** and N-benzyloxy-N-methyl-glutaramide as a colourless foam, yield 79%. $[\alpha]_D^{20}$ +47.6 (c 10.0 chloroform). MS (ESI) m/z 1137.0 $[M+H]^+$, 1159.8 $[M+Na]^+$.

*Methyl 2,3,4-tris-O-[4-(N-benzyloxy-N-n-butylcarbamoyl)-n-butyryl]-6-O-trityl-α-D-glucopyranoside (**6d**) $C_{74}H_{91}N_3O_{15}$* (1262,56)
The compound was prepared analogously to **6a** from **1** and N-benzyloxy-N-n-butyl-glutaramide (2 d stirring). The colourless foam was nearly pure (TLC), yield 87%. MS (ESI) m/z 1262 $[M+H]^+$, 1284 $[M+Na]^+$.

*Methyl 2,3,4-tris-O-[4-(N-benzoyloxy-N-methylcarbamoyl)-n-butyryl]-6-O-trityl-α-D-galactopyranoside (**7a**) $C_{65}H_{67}N_3O_{18}$* (1178.27)
The compound was prepared similar to 6a from methyl 6-*O*-triphenylmethyl-α-D-galactopyranoside (**2**) and N-benzoyloxy-N-methyl-glutaramide as a colourless foam, yield 89%. $[\alpha]_D^{20}$ +46.7 (c 10.0 methanol). MS

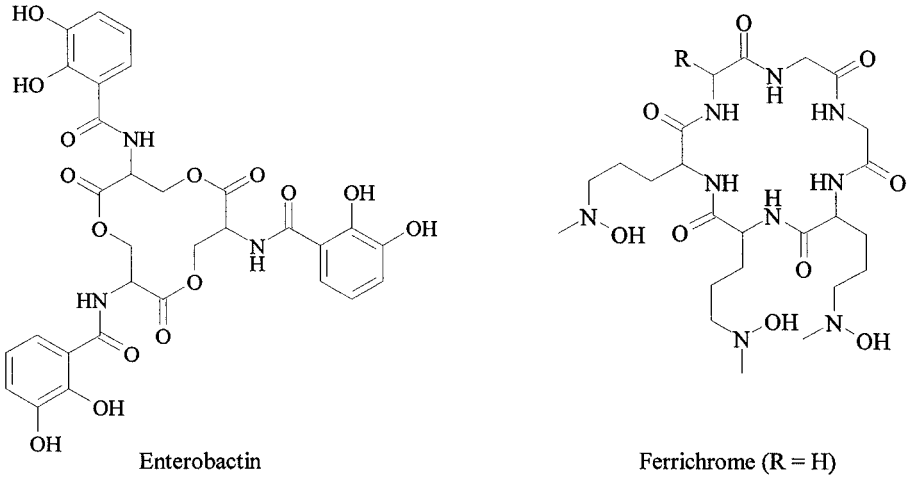

Fig. 1. Bacterial siderophores as models for new syntheses of trishydroxamates and catecholates.

(ESI) m/z 1178.5 $[M+H]^+$, 1201.7 $[M+Na]^+$.

*Methyl 2,3,4-tris-O-[3-(N-benzyloxy-N-methylcarbamoyl)-n-propionyl]-6-O-trityl-α-D-galactopyranoside(***7b***),* $C_{62}H_{67}N_3O_{15}$ (1094.24)
The compound was prepared similar to **6a** from **2** and N-benzyloxy-N-methyl-succinamide as a colourless foam, yield 81%. $[\alpha]_D^{20}$ + 46.3 (c 8.5 methanol). MS (ESI) m/z 1094.8 $[M+H]^+$, 1117.8 $[M+Na]^+$.

*Methyl 2,3,4-tris-O-[4-(N-benzyloxy-N-methylcarbamoyl)-n-butyryl]-6-O-trityl-α-D-galactopyranoside (***7c***)* $C_{65}H_{73}N_3O_{15}$ (1136.32)
The compound was prepared similar to **6a** from **2** and N-benzyloxy-N-methyl-glutaramide as a colourless foam, yield 75%. $[\alpha]_D^{20}$ + 47.4 (c 5.0 methanol). MS (ESI) m/z 1136.7 $[M+H]^+$, 1158.8 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzoyloxy-N-methylcarbamoyl)-n-butyryl]-α-D-glucopyranoside-
*(***8a***)* $C_{46}H_{53}N_3O_{18}$ (935.94)
Compound **6a** (350 mg, 0.3 mmol) was dissolved in dichloromethane (50 ml) and boron trifluoride etherate (90 mg, 0.6 mmol) was added at r.t.. The reaction was finished after about 40 min, until no educt was shown at TLC (3:1:0.5-chloroform- ethyl acetate-acetic acid). Then water was added. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated. Purification followed by HPLC and **8a** was afforded as white foam (570 mg, 70%). $[\alpha]_D^{20}$ +49.8 (c 8.0 chloroform). ^{1}H-NMR ($CDCl_3$): 1.78–1.90 (m, 6H, CH_2), 2.21–2.35 (m, 12 H, CH_2CO), 3.30 (s, 3H, αOCH_3), 3.32 (s, 3H, NCH_3), 3.34 (s, 6H, NCH_3), 3.53–3.69 (m, 3H, H5, H6, H6′), 4.71 (dd, J = 3.6, 10.2, 1H, H2), 4.87 (d, J = 3.7, 1H, H1), 4.89 (t, J = 11, 1H, H4), 5.42 (t, J = 9.8, 1H, H3), 7.45–7.50 (m, 6H, aromatic H), 7.61–7.63 (m, 3H, aromatic H), 8.01–8.05 (m, 6H, aromatic H). MS (ESI) m/z 936.3 $[M+H]^+$, 958.7 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[3-(N-benzyloxy-N-methylcarbamoyl)-n-propionyl]-α-D-glucopyranoside
*(***8b***)* $C_{43}H_{53}N_3O_{15}$ (851.91)
The compound was prepared similar to **8a** from **6b** as a colourless foam, yield 49%. $[\alpha]_D^{20}$ +48.2 (c 8.3, chloroform). MS (ESI) m/z 852.3 $[M+H]^+$, 874.2 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzyloxy-N-methylcarbamoyl)-n-butyryl]-α-D-glucopyranoside
*(***8c***)* $C_{46}H_{59}N_3O_{15}$ (893.99)
The compound was prepared similar to **8a** from **6c** (reaction time 1 h) as a colourless foam, yield 70%. $[\alpha]_D^{20}$ +45.6 (c 10.0, chloroform). MS (ESI) m/z 894.8 $[M+H]^+$, 916.9 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[3-(N-hydroxy-N-methylcarbamoyl)-n-propionyl]-α-D-glucopyranoside
*(***8d***)* $C_{22}H_{35}N_3O_{15}$ (581.54)
Compound **8b** (150 mg, 0.18 mmol) was dissolved in methanol and hydrogenated for 2 h with Pd/C (10%, 20%w/w) at ambient temperature and atmospheric pressure to give a yellow oil, yield 88% (92 mg). $[\alpha]_D^{20}$ +59.0 (c 10 methanol). ^{1}H-NMR (CD_3OD):

2.60–2.77 (m, 12H, CH_2), 3.19 (s, 3H, NCH_3), 3.26 (s, 6H, NCH_3), 3.42 (s, 3H,O-CH_3), 4.07 (t, J = 6.0, 1H), 4.11 (d, J = 2.1, 1H), 4.25 (d, J = 5.5, 1H), 4.9 (d, J = 3.5, 1H), 5.24 (dd, J = 2.7, 10.8, 1H), 5.28 (dd, J = 3.5, 10.3, 1H). MS (ESI) m/z 582.4 $[M+H]^+$, 604.2 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-hydroxy-N-methylcarbamoyl)-n-butyryl]-α-D-glucopyranoside
*(***8e***)* $C_{25}H_{41}N_3O_{15}$ (623.62)
The compound was prepared similar to **8d** from **8c** (reaction time 3 h) as a yellow oil, yield 75%. $[\alpha]_D^{20}$ +64.0 (c 10 methanol). MS (ESI) m/z 624.5 $[M+H]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzyloxy-N-n-butylcarbamoyl)-n-butyryl]-α-D-glucopyranoside
*(***8f***)* $C_{55}H_{77}N_3O_{15}$ (1019,23)
The compound was prepared analogously to **8a** from **6d** (reaction time 5 h) resulting a colourless foam. After silica gel column chromatography yielded 49%. MS (ESI) m/z 1020 $[M+H]^+$, 1042 $[M+Na]^+$.

Methyl 2,3,4-tris-O[4-(N-hydroxy-N-n-butylcarbamoyl)-n-butyryl]-α-D-glucopyranoside
*(***8g***)* $C_{34}H_{59}N_3O_{15}$ (749,86)
The compound was prepared analogously to 8d from 8f (reaction time 2 h) as a colourless oil, yield 85%. $[\alpha]_D^{20}$ +63,19° (c = 11,9 mg/ml). MS (ESI) m/z 750 $[M+H]^+$, 772 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzoyloxy-N-methylcarbamoyl)-n-butyryl]-α-D-galactopyranoside
*(***9a***)* $C_{46}H_{53}N_3O_{18}$ (935.94)
The compound was prepared similar to **8a** from **7a** (reaction time 1.5 h) as a colourless foam, yield 89%. $[\alpha]_D^{20}$+ 49.0 (c 10 methanol). MS (ESI) m/z 936.5 $[M+H]^+$, 958.8 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[3-(N-benzyloxy-N-methylcarbamoyl)-n-propionyl]-α-D-galactopyranoside
*(***9b***)* $C_{43}H_{53}N_3O_{15}$ (851.91)
The compound was prepared similar to **8a** from **7b** (reaction time 1 h) as a colourless foam, yield 53%. $[\alpha]_D^{20}$ +48.4 (c 10.0, methanol). MS (ESI) m/z 852.4 $[M+H]^+$ 874.3 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzyloxy-N-methylcarbamoyl)-n-butyryl]-α-D-galactopyranoside
*(***9c***)* $C_{46}H_{59}N_3O_{15}$ (893.99)
The compound was prepared similar to **8a** from **7c** (reaction time 2 h) as a colourless foam, yield 47%. $[\alpha]_D^{20}$ +47.1 (c 5.0 methanol). MS (ESI) m/z 894.6 $[M+H]^+$, 916.7 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[3-(N-hydroxy-N-methylcarbamoyl)-n-propionyl]-α-D-galactopyranoside
*(***9d***)* $C_{22}H_{35}N_3O_{15}$ (581.54)
The compound was prepared similar to **8d** from **9b** (reaction time 2 h) as a yellow oil, yield 84%. $[\alpha]_D^{20}$ +58.4 (c 5.0, methanol). MS (ESI) m/z 582.2 $[M+H]^+$, 604.2 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-hydroxy-N-methylcar bamoyl)-n-butyryl]-α-D-galactopyranoside
*(***9e***)* $C_{25}H_{41}N_3O_{15}$ (623.62)
The compound was prepared similar to **8d** from **9c** (reaction time 3.5 h) as a yellow oil, yield 89%. $[\alpha]_D^{20}$ +62.7 (c 10, methanol). MS (ESI) m/z 624.4 $[M+H]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzoyloxy-N-methylcarbamoyl)-n-butyryl]-α-D-ribopyranoside
*(***10a***)* $C_{45}H_{51}N_3O_{17}$ (905.52)
The compound was prepared similar to **6a** from methyl-α-D-ribopyranoside 3 and *N*-benzoyloxy-*N*-methyl-glutaramide as a colourless foam, yield 35%. $[\alpha]_D^{20}$ +16.5 (c 10.0 methanol). MS (ESI) m/z 906.4 $[M+H]^+$, 928.3 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[3-(N-benzyloxy-N-methylcarbamoyl)-n-propionyl]-α-D-ribopyranoside
*(***10b***)* $C_{42}H_{51}N_3O_{14}$ **(821.89)**
The compound was prepared similar to **6a** from **3** and *N*-benzyloxy-*N*-methyl-succinamide as a colourless foam, yield 38%. $[\alpha]_D^{20}$ +8.4 (c 10.0 chloroform). MS (ESI) m/z 821.8 $[M+H]^+$, 844.0 $[M+H]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzyloxy-N-methylcarbamoyl)-n-butyryl]-α-D-ribopyranoside
*(***10c***)* $C_{45}H_{57}N_3O_{14}$ (863.97)
The compound was prepared similar to **6a** from **3** and *N*-benzyloxy-*N*-methyl-glutaramide as a colourless foam, yield 24%. $[\alpha]_D^{20}$ +12.6 (c 5.0 chloroform) MS (ESI) m/z 864.5 $[M+H]^+$, 886.7 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[3-(N-hydroxy-N-methylcarbamoyl)-n-propionyl]-α-D-ribopyranoside
*(***10d***)* $C_{21}H_{33}N_3O_{14}$ (551.51)
The compound was prepared similar to **8d** from **10b** (reaction time 1.5 h) as a light yellow oil, yield 50%. $[\alpha]_D^{20}$ +23.2 (c 3.5 methanol). MS (ESI) m/z 552.4

$[M+H]^+$, 574.3 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzoyloxy-N-methylcarbamoyl)-n-butyryl]-α-D-xylopyranoside
(**11a**) $C_{45}H_{51}N_3O_{17}$ (905.52)
The compound was prepared similar to **6a** from methyl α-D-xylopyranoside **4** and *N*-benzoyloxy-*N*-methyl-glutaramide as a colourless foam, yield 46%. $[\alpha]_D^{20}$ +8.6 (c 10.0 chloroform). MS (ESI) m/z 906.2 $[M+H]^+$, 928.4 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[3-(N-benzyloxy-N-methylcarbamoyl)-n-propionyl]-α-D-xylopyranoside
(**11b**) $C_{42}H_{51}N_3O_{14}$ (821.89)
The compound was prepared similar to **6a** from **4** and *N*-benzyloxy-*N*-methyl-succinamide as a colourless foam, yield 32%. $[\alpha]_D^{20}$ +4.0 (c 10 chloroform). MS (ESI) m/z 822.4 $[M+H]^+$, 844.6 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-benzyloxy-N-methylcarbamoyl)-n-butyryl]-α-D-xylopyranoside
(**11c**) $C_{45}H_{57}N_3O_{14}$ (863.97)
The compound was prepared similar to **6a** from **4** and *N*-benzyloxy-*N*-methyl-glutaramide as a colourless foam, yield 43%, $[\alpha]_D^{20}$ +7.9 (c 5.0, chloroform). MS (ESI) m/z 864.7 $[M+H]^+$, 886.4 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[3-(N-hydroxy-N-methylcarbamoyl)-n-propionyl]-α-D-xylopyranoside
(**11d**) $C_{21}H_{33}N_3O_{14}$ (551.51)
The compound was prepared similar to **8d** from **10b** (reaction time 1 h) as a light yellow oil, yield 70%. $[\alpha]_D^{20}$ +26.4 (c 5.0 methanol). MS (ESI) m/z 552.2 $[M+H]^+$, 574.3 $[M+Na]^+$.

Methyl 2,3,4-tris-O-[4-(N-hydroxy-N-methylcarbamoyl)-n-butyryl]-α-D-xylopyranoside
(**11e**) $C_{24}H_{39}N_3O_{14}$ (593.59)
The compound was prepared similar to **8d** from **10c** (reaction time 2 h) as a light yellow oil, yield 87%. $[\alpha]_D^{20}$ +24.1 (c 1.0 methanol). MS (ESI) m/z 594.3 $[M+H]^+$, 616.4 $[M+Na]^+$.

2,4,6-Tris-O-[4-(N-benzoyloxy-N-methylcarbamoyl)-n-butyryl]-1,3,5-tris-O-benzyl-myo-inositol
(**12a**) $C_{66}H_{69}N_3O_{18}$ (1192.30)
The compound was prepared similar to **6a** from *1,3,5-tris-O-benzyl-myo-inositol* **5** and *N*-benzoyloxy-*N*-methylglutaramide as a colourless foam, yield 85%. MS (ESI) m/z 1214.9 $[M+Na]^+$.

2,4,6-Tris-O-[3-(N-benzyloxy-N-methylcarbamoyl)-n-propionyl]-1,3,5-tris-O-benzyl-myo-inositol
(**12b**) $C_{63}H_{69}N_3O_{15}$ (1108.26)
The compound was prepared similar to **6a** from **5** and *N*-benzyloxy-*N*-methyl-succinamide as a colourless foam, yield 67%. MS (ESI) m/z 1108.4 $[M+H]^+$, 1130.6 $[M+Na]^+$.

2,4,6-Tris-O-[4-(N-benzyloxy-N-methylcarbamoyl)-n-butyryl]-1,3,5-tris-O-benzyl-myo-inositol
(**12c**) $C_{66}H_{75}N_3O_{15}$ (1150.34)
The compound was prepared similar to **6a** from **5** and *N*-benzyloxy-*N*-methyl-glutaramide as a colourless foam, yield 75%. MS (ESI) m/z 1151.0 $[M+H]^+$, 1173.3 $[M+Na]^+$.

2,4,6-Tris-O-[3-(N-hydroxy-N-methylcarbamoyl)-n-propionyl]-1,3,5-tris-O-benzyl-myo-inositol
(**12d**) $C_{42}H_{51}N_3O_{15}$ (837.89)
The compound was prepared similar to **8d** from **12b** (reaction time 8 h) as a colourless oil, yield 92%. MS (ESI) m/z 838.7 $[M+H]^+$, 860.5 $[M+Na]^+$.

2,4,6-Tris-O-[4-(N-hydroxy-N-methylcarbamoyl)-n-butyryl]-1,3,5-tris-O-benzyl-myo-inositol
(**12e**) $C_{45}H_{57}N_3O_{15}$ (879.97)
The compound was prepared similar to **8d** from **12c** (reaction time 12 h) as a colourless oil, yield 89%. MS (ESI) m/z 880.6 $[M+H]^+$, 902.5 $[M+Na]^+$.

Methyl 2,3,4-tris-O-{N-[3-(8-methoxycarbonyloxy-3,4-dihydro-2H-1,3-benzoxazin-3yl)-propionyl]-aminopropyl}-6-O-trityl-α-D-glucopyranoside
(**14**) $C_{74}H_{76}N_6O_{27}$, (1481,45)
The compound was prepared simlar to the corresponding *methyl 2,3,4-tris-O-{N-[3-(8-methoxycarbonyloxy-3,4-dihydro-2H-1,3-benzoxazin-3yl)-acetyl]-aminopropyl}-6-O-trityl-α-D-glucopyranoside* (Heggemann *et al.* 2001) as yellow foam, yield 27%. MS (ESI) m/z 1481.5 $[M+H]^+$, 1503.3 $[M+Na]^+$.

Methyl 2,3,4-tris-O-{N-[N-(2,3-dihydroxybenzoyl)-β-alanyl]-aminopropyl}-α-D-glucopyranoside (**15c**)
$C_{46}H_{62}N_6O_{18}$ (987.04)
Compound 14 (1.2 g, 0.8 mmol) was added to 2 M sodium hydroxide (5 ml), which was blubbered with nitrogen for about ten minutes. The reaction mixture was stirred at r.t. for 1 h and neutralized with 1 M HCl. A grey solid was precipitated, which was filtered and washed with water. The residue was dissolved in ethyl acetate and the extract washed with brine and

water, dried over Na_2SO_4, filtered and evaporated. Methyl 2,3,4-tris-O-{*N*-[*N*-(2,3-dihydroxybenzoyl)-β-alanyl]-aminopropyl}-6-O-trityl-α-D-glucopyranoside (620 mg, 63%) was afforded (TLC, 3:1:0.5 chloroform-ethyl acetate-acetic acid, R_f = 0.15). This intermediate product was dissolved in dichloromethane (40 ml) and boron trifluoride etherate (72 mg, 0.5 mmol) in methanol (0.2 ml) was added at r.t.. The reaction was finished after about 40 min, until no educt was shown at TLC (3:1:0.5- chloroform-ethyl acetate- acetic acid). **15c** was afforded as white foam (230 mg, yield 29%). $[\alpha]_D^{20}$ +28.6°(c 9.2, methanol). ^{1}H-NMR ($CDCl_3$): 1.54–1.74 (m, 6H, -CH_2-), 2.4–2.6 (m, 6H, CH_2N), 2.9–3.9 (m, 24 H), 3.32 (s, α OCH_3), 3.34 (s, 6H, CH_2NH), 3.39 (s, 6H, CH_2-CO), 4.8 (d, J = 3.4, H1), 6.51–6.90 (m, 6H, NH), 6.97–7.23 (m, 9H, aromatic H). MS (ESI) m/z 987.5 $[M+H]^+$, 1009.9 $[M+Na]^+$.

Methyl 2,3,4-tris-O-(3-aminopropyl)-6-O-trityl-α-D-galactopyranoside (**16**), $C_{35}H_{49}N_3O_6$, (607.8)
The compound was prepared similar to the corresponding methyl α-*D*-glucopyranoside derivative (Heggemann *et al.* 2001) as a white foam, yield 60%, $[\alpha]_D^{20}$ +48.4 (c 10.0 methanol). MS (ESI) m/z 608.3 $[M+H]^+$, 646.1 $[M+K]^+$.

*Methyl 2,3,4-tris-O-[N-(2,3-diacetoxybenzoyl)-amino-propyl]-6-O-trityl-α-D-galacto-pyranoside (***17***),* $C_{68}H_{73}N_3O_{21}$ (1268.4)
The compound was prepared similar to the corresponding α-*D*-*glucopyranoside* derivative (Heggemann *et al.* 2001) as white foam, yield 40%. TLC (3:1:0.5 chloroform-ethylacetate-acetic acid) R_f = 0.47. $[\alpha]_D^{20}$ +12.0 (c 5.0 methanol). MS (ESI) m/z 1290.3 $[M+Na]^+$.

*Methyl 2,3,4-tris-O-[2-(2,3-dihydroxybenzylidene-hydrazinocarbonyl)-ethyl]-α-D-glucopyranoside (***19a***)* $C_{37}H_{44}N_6O_{15}$ (812.79)
A solution of methyl 2,3,4-tris-*O*-[2-(carboxymethyl)-ethyl]-α-*D*-glucopyranoside **18** (100 mg, 0.22 mmol) in 0.5 ml water was treated with hydrazine hydrate (80%, 0.5 ml) and the mixture was heated for 1 h and then evaporated. The residue was dissolved in acetic acid (2 ml) and 2,3-dihydroxybenzaldehyde (138 mg, 0.53 mmol) was added. The solution was heated for 2 h. The raw product was filtered off, washed with water free from acid, dissolved in diethylether, dried over Na_2SO_4, filtered and evaporated. Purification by HPLC afforded 90 mg of **19a** (50%). ^{1}H-NMR (DMSO-d_6): 2.45–2.49 (m, 4H, CH_2CO), 2.82–2.97 (m, 2H, CH_2CO), 3.22–3.25 (m, 4H, αOCH_3, CH), 3.34–3.48 (m, 8H, OCH_2, CH) 3.82–3.89 (m, 3 H), 4.74 (d, J = 3.0, 1H, H1), 6.65–7.11 (m, 9 H, aromatic H), 8.28 (d, J = 3.2, 3H, = CH-), 9.11 (br, 3H, C-OH), 9.37 (br, 3H, C-OH), 11.61–11.67 (3s, 3H, NH), MS (ESI) m/z 813.3 $[M+H]^+$, 835.5 $[M+Na]^+$.

*Methyl 2,3,4-tris-O-{2-[2,3-di(methoxycarbonyloxy) benzyli denehydrazinocarbonyl]-ethyl}-α-D-glucopyrano side (***19b***)* $C_{49}H_{56}N_6O_{27}$ (1161.02)
The compound was prepared similar to **19a** from **18** and 2,3-di(methoxycarbonyloxy)benzaldehyde (prepared like Rosenmund, 1926), yield: 54%, $[\alpha]_D^{20}$ +24.6 (c 7.5, methanol). MS (ESI) m/z 1161.8 $[M+H]^+$, 1184.2 $[M+Na]^+$.

Determination of siderophore activity

Utilization of siderophores was determined by growth promotion assays according to Schumann & Möllmann (2000) and Heinisch *et al.* (2002b). Siderophore analogues were applied at 10 μmol on assay discs of 6 mm in diameter on the surface of the inoculated agar plates. Desferrioxamin B (Desferal mesylate, Sigma, Germany), ferricrocin and ferrichrome (kindly supplied by H-P Fiedler, Tübingen, Germany) were used as a control. The growth zones around the discs were read after incubation for 24–48 h at 37 °C. The following Gram-negative bacteria were used: the wild type strains *Pseudomonas aeruginosa* ATCC 27853, SG 137, NCTC 10662, ATCC 9027, K799/WT, *Escherichia coli* ATCC 25922 and the enterobactin-deficient mutant *Salmonella typhimurium* enb7 (Table 1).

Moreover, we tested the new compounds for growth promotion of mycobacteria, using the wild type strain of *Mycobacterium smegmatis* mc^2155 and it's iron transport mutants M24 (deficient in mycobactin biosynthesis), B1 (deficient in exochelin biosynthesis), B3 (deficient in mycobactin and exochelin biosynthesis) and U3 (deficient in mycobactin biosynthesis and exochelin uptake) (Schumann *et al.* 1998; Schumann & Möllmann 2000). Mycobactin and ferrichrome were used as a control. The synthesized compounds were applied as desferrisiderophores and some compounds additionally as iron complexes (ferrisiderophores + Fe). The iron complexes were prepared by titration of the corresponding desferrisiderophore with $FeCl_3$ and simultaneously control

Table 1. Growth promotion of Gram negative bacteria, diameter of growth zone (mm), substance application 10 μmol on 6 mm paper discs.

Compound	*Pseudomonas aeruginosa*					*E. coli*	*S. typhimurium*	CAS Assay[c]
	ATCC 27853	SG 137	NTCC 10662	ATCC 9027	K799/ WT	ATCC 25922	enb 7	
6a	0	0	0	0	0	0	0	−
7a	0	0	0	0	0	0	0	−
8a	0	0	0	0	0	13	0	−
8d	18	20	25	19	20	22	12	++
8e	11	20	19	14	11	16	10	+
8g	22	20	20	20	22	23	19	++
9a	0	0	11	0	0	0	0	−
9d	0	19	14	15	10	17	0	+
9e	21	25	28	26	25	19	28	++
10a	0	0	0	0	0	0	0	−
10d	24	24	24	22	18	26	17	++
11a	0	0	0	0	0	0	0	−
11d	17	25	24	20	25	23	17	++
11e	20	24	29	26	28	27	27	++
12a	0	0	0	0	0	0	0	−
12d	0	0	0	0	0	0	0	++
12e	0	0	0	0	0	0	0	++
14	14	12	11	10	15	0	0	−
15a	23	22	26	24	25	26	27	++
15b	23	24	24	26	24	19	23	++
15c	25	21	28	n.d.	23	27	20	++
17	20	23	25	n.d.	23	26	26	++
19a	25	23	25	22	20	15	14	++
19b	16	18	17	0	15	0	0	+
control	35[a]	30[a]	31[a]	34[a]	35[a]	33[b]	32[a]	

[a]desferal, [b]ferricrocin; [c] - no CAS reaction, + weak CAS reaction, ++ strong CAS reaction. n.d. = not determined.

of the CAS reaction to make sure that there is no surplus of ferric ions (Table 2).

The recognition and uptake specificity of the siderophores was studied by use of *E. coli* K12 mutants with alterations in the TonB protein, which transfers energy essentially for all active iron transport systems in Gram-negative bacteria, and in the catecholate siderophore receptors FepA, Cir and Fiu (Hantke 1990). For the *E. coli* mutants the following assay medium was used: NaCl 0.5%, Tryptone 0.8%, agar 1%, 150 μmol dipyridyl and 150 μmol ED-DHA. 2,3-Dihydroxybenzoic acid (2,3-DHBA) and ferricrocin were used as control (Table 3).

In parallel to the growth promotion assays the relative iron complexing capacity of the siderophore derivatives was checked by the chromazurol-S (CAS) assay according to Schwyn & Neilands (1987). A positive CAS reaction is associated with iron chelation (Table 1).

Results and discussion

Synthesis of trishydroxamates

We started from methyl 6-O-trityl-α-D-glucopyranoside **1**, methyl 6-O-trityl-α-D-galactopyranoside **2**, methyl α-D-ribopyranoside **3**, methyl α-D-xylopyranoside **4** and 1,3,5-tris-O-benzyl-*myo*-inositol **5** for the synthesis of trishydroxamates with a carbohydrate backbone. The trityl derivatives **1** and **2** were prepared from methyl α-D-glucopyranoside and methyl α-D-galactopyranoside with triphenylchloromethane in DMF (Chaudhary *et al.* 1979). The compounds **3** and **4** were synthesized from D-ribose and

Table 2. Growth promotion of mycobacteria, diameter of growth zone (mm), substance application 10 μmol (mycobactin 2 μg) on 6mm paper discs.

Compound	mc^{2}155		M24		B1		B3		U3	
		+Fe		+Fe		+Fe		+Fe		+Fe
6a	0		0		0		0		0	
7a	0		0		0		0		0	
8a	0		0		7		0		0	
8d	0	18	0	22	0	21	0	15	0	16
8e	0	24	0	27	0	27	0	12	0	12
8g	25	28	0	19	26	25	0	13	0	12
9a	9		0		0		0		0	
9d	0	22	0	15	0	21	0	13	0	0
9e	0	36	0	33	0	36	0	28	0	26
10a	0		8		0		0		0	
10d	0	33	0	32	0	30	0	19	0	24
11a	8		0		0		0		0	
11d	0	30	0	24	0	25	0	18	0	20
11e	0	34	0	31	18	33	0	15	0	17
12a	0		0		0		0		0	
12d	11	15	0	16	15	17	0	0	0	0
12e	18	15	0	19	22	10	0	0	0	0
14	10		0		0		0		0	
15a	20	32	0	27	18	30	0	16	0	15
15b	15	23	8	22	14	23	0	0	0	0
15c	24	30	0	18	21	32	0	14	0	13
17	22	27	0	16	22	23	0	0	0	0
19a	0	29	0	20	0	26	0	0	0	0
19b	0	26	0	21	0	21	0	0	0	0
Ferrichrome		30		28		32		25		22
Mycobactin		14		16		15		15		16

Table 3. Growth promotion of E.coli wild type strains and mutants by selected derivatives. Diameter of growth zone (mm), substance application 10 μmol.

Compound		AB 2847	BR 158	H1443	H1876	H873	H1877	H1875
	TonB	+	−	+	+	+	+	+
	FepA	+	+	+	−	−	−	−
	Cir	+	+	+	−	+	+	−
	Fiu	+	+	+	−	+	−	+
9e		23	0	23	24	21	22	23
11e		24	0	25	26	25	27	27
15a		32	0	32	0	27	25	25
15b		25	0	26	0	25	25	22
15c		25	0	25	0	24	21	22
17		29	0	31	0	27	25	25
2,3-DHBA[a]		30	0	32	0	30	27	30
Ferricrocin		30	0	30	30	31	32	33

[a] 2,3 DHBA = 2,3-dihydroxybenzoic acid.

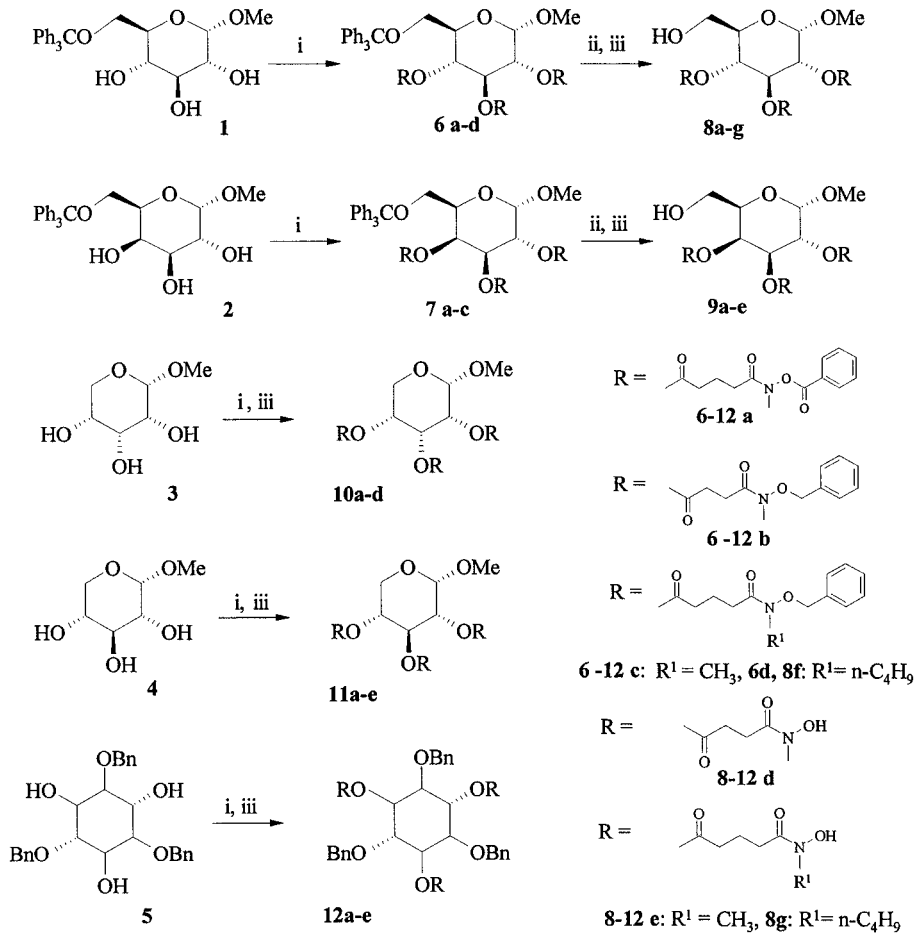

Fig. 2. Synthesis of trishydroxamates **6–12** based on methyl α-*D*-glucopyranoside (6-O-tritylderivative = **1**), methyl α-D-galactopyranoside (6-tritylderivative = **2**), methyl α-D-ribopyranoside **3**, methyl α-D-xylopyranoside **4** and 1,3,5-tri-O-benzyl-*myo*-inositol **5**. Synthesis: (i) DCC, DMAP, CH_2Cl_2; (ii) BF_3-etherate/ methanol, CH_2Cl_2; (iii) H_2, Pd/C, methanol.

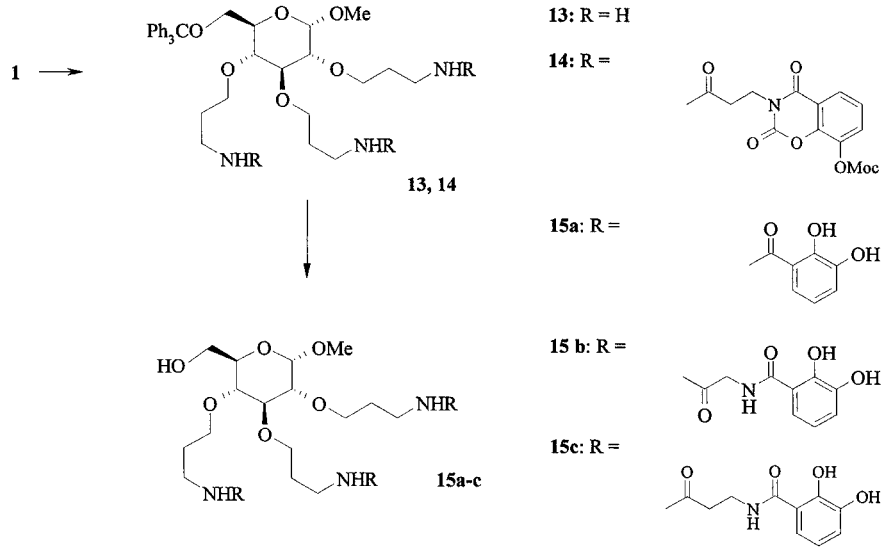

Fig. 3. Synthesis and structure of triscatecholates of methyl α-*D*-glucopyranoside **14-15**, Moc = $COOCH_3$.

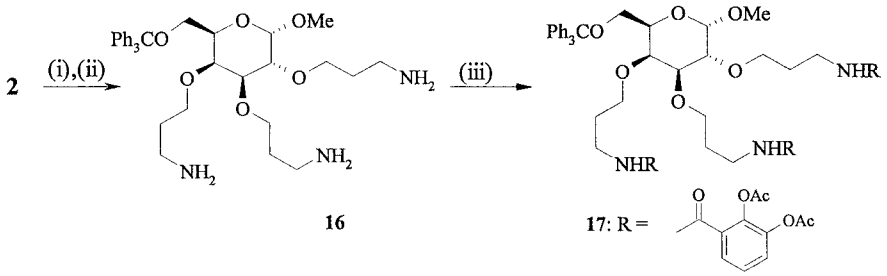

Fig. 4. Synthesis and structure of the triscatecholate **17** based on methyl α-D-galactopyranoside **17**, Ac = $COCH_3$ (i) acrylonitrile, 1 M KOH; (ii) $NaBH_4$, $CoCl_2$, methanol; (iii) R-Cl, triethylamine, DMAP, anhydrous tetrahydrofuran.

D-xylose by the Fisher glycosidation in methanol using ion exchange resins (Bishop *et al.* 1963; Mowery 1963). Compound **5** was prepared from *myo*-inositol according to Billington *et al.* (1989). The formation of the ester bonds of the protected hydroxamates **6a–d, 7a–c, 10a–d, 11a–c, 12a–c** followed the Steglich method (Neises & Steglich 1978) by the use of *N*-benzoyloxy-*N*-methylglutaramide (Wittmann *et al.* 2002), *N*-benzyloxy-*N*-methylsuccinamide, *N*-benzyloxy-*N*-methyl-glutaramide (Sharma *et al.* 1989) and N-benzyloxy-N-n-butyl-glutaramide (prepared by the same manner) with dicyclohexylcarbodiimide (DCC), *N*, *N*-dimethylamino-pyridine (DMAP) in dichloromethane. The removal of the trityl group of the compounds **6a–d** and **7a–c** by a methanolic solution of BF_3-etherate in dichloromethane (Dax *et al.* 1978) afforded the compounds **8a–c, f** and **9a–c**.

The free trishydroxamate compounds of the various carbohydrates **8d, e, g; 9d, e; 10d; 11d, e; 12d, e** were yielded by catalytic hydrogenolysis of the benzyloxy groups with Pd/C in methanol at atmospheric pressure and ambient temperature (Figure 2).

Synthesis of triscatecholates

Synthesis of triscatecholates of methyl α-D-glucopyranoside. We synthesized some new triscatecholates based on methyl α-*D*-glucopyranoside with free catecholic OH-groups and different spacer groups in addition to our previous publication (Heggemann *et al.* 2001). The synthesis of the compounds **15a** and **15b** was described previously by Dhungana *et al.* 2001. The siderophore analogue with the longer spacer unit was synthesized by reaction of methyl 2,3,4-tri-O-(3-aminopropyl)-6-O-trityl-α-*D*-glucopyranoside **13** (Heggemann *et al.* 2001) with 3-(8-methoxycarbonyloxy-3,4-dihydro-2H-1,3-benzoxazin-3-yl)-propionyl chloride (Wittmann *et al.* 1999) to obtain the O-trityl-derivative **14**. This compound was hydrolyzed with 1 M sodium hydroxide under N_2-atmophere to give the free catecholate. The removal of the trityl group by boron trifluoride afforded methyl 2,3,4-tris-O-{*N*-[*N*-(2,3-dihydroxybenzoyl)-β-alanyl]-aminopropyl}-α-*D*-glucopyranoside **15c** (Figure 3).

Synthesis of triscatecholates of methyl α-D-galactopyranoside. We prepared corresponding methyl α-D-galactopyranoside derivatives to compare the siderophore activity of the triscatecholate glucopyranoside derivatives with other monosaccharide based siderophores. The methyl 2,3,4-tris-O-(N-2,3-diacetoxy-benzoyl-aminopropyl}-6-O-trityl-α-D-galactopyranoside **17** was synthesized similar to the corresponding methyl α-*D*-glucopyranoside derivative (Heggemann *et al.* 2001). In a Michael type cyanoethylation reaction methyl 6-O-trityl α-D-galactopyranoside was treated with acrylonitrile and potassium hydroxide to yield methyl (2-cyanoethyl)-6-O-trityl-α-D-galactopyranoside. The three nitrile groups were reduced by $NaBH_4$ when $CoCl_2$ as catalyst in a methanolic solution was added. This obtains methyl 2,3,4-tris-O-(3-aminopropyl)-6-O-trityl-α-D-galactopyranoside **16**, which reacted with 2,3-di(acetoxy)benzoyl chloride (Rastetter *et al.* 1981) to give compound **17** (Figure 4).

*Synthesis of 2,3,4-tris-[2-{2,3-dihydroxybenzylidene-hydrazinocarbonyl)-ethyl] derivatives of methyl α-D-glucopyranoside (***19a,b***).* We replaced the aminopropyl groups of compounds **13–17** with hydrazinocarbonylethyl functional groups as a new variation of the carbohydrate siderophores. The starting-material was methyl 2,3,4-tris-O-[2-(carboxymethyl) ethyl]-α-*D*-glucopyranoside **18** (Bazin *et al.* 1995) prepared from methyl 2,3,4-tris-O-(2-cyanoethyl)-6-O-trityl-α-*D*-glucopyranoside with a methanolic solution of hydrochloric acid (Mori 1974). This com-

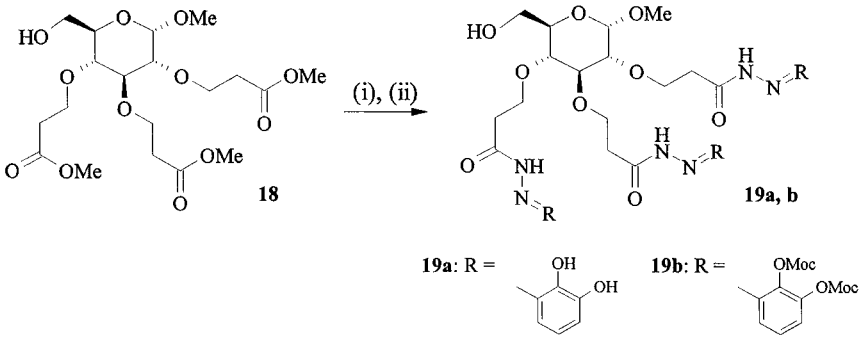

Fig. 5. Synthesis of *2,3,4-tris-[2-(2,3-dihydroxybenzylidenehydrazinocarbonyl)-ethyl] derivatives of methyl α-D-glucopyranoside* **19a,b**, Moc = $COOCH_3$; (i) hydrazine hydrate, δ; (ii) R-CHO, ethylacetate.

pound was treated with hydrazine hydrate (80%) to give the intermediate methyl 2,3,4-tris-O-[2-(3-hydrazinocarbonylethyl)]-α-D-glucopyranoside (**19**, R = H), which reacted with 2,3-dihydroxybenzaldehydes and with 2,3-di(methoxycarbonyloxy)-benzaldehyde to give the compounds **19a** and **b**. (Figure 5). We synthesized also the corresponding 3,4-dihydroxyderivatives, but these compounds were inactive in our tests.

Siderophore activity

The siderophore activity of the synthesized compounds was determined by a growth promotion assay under iron limitation using wild type strains of Gram-negative bacteria and the enterobactin mutant *S. typhimurium* enb 7 (Table 1). The benzyloxy derivatives **6–12b, c** and **6d** as educts for the corresponding free trishydroxamates were not tested, because iron complexation is impossible. The trishydroxamates with benzoyloxy groups **6a–12a** did not exhibit any relevant activity. Compounds **10a** and **11a** were completely inactive, also the tribenzyl *myo*-inositol derivatives **12d, e** due to their larger size and their unpolarity. The free trishydroxamates **8d, e, g, 9d, e, 10d**, and **11d, e** were active on all test strains. Apparently there is a joint influence of the length of the spacer groups and of the individual sugar backbone component. The galactose derivative with longer spacer group **9e** was more active than the compound with shorter spacer group **9d**. Otherwise the glucose derivative **8d** with a shorter spacer was more active than **8e** with a longer spacer. The same is valid for the activity of **8d, e** and **9d, e** on mycobacteria, but only by using the preformed iron complexes of the derivatives (Table 2). The free OH groups of the triscatecholates **15a–c** and the acetylated compound **17** allowed effective iron complexation and siderophore activity in contrast to the corresponding benzoxazine derivative **14**. The benzylidenhydrazino derivatives **19a** (with 2,3-OH groups) and **19b** (with methoxycarbonyloxy groups) exhibited preferred activity on *P. aeruginosa* strains.

Growth promoting activity of the trishydroxamates as desferricompounds on mycobacteria (Table 2) is concentrated on glucose and *myo*-inositol derivatives. Compound **8g** bearing a lipophilic butyl component and the tribenzyl *myo*-inositol derivatives **12d** and **e** were active on the wild type strain mc^2155 and on the mutant B1. In contrast to all other strains, both mc^2155 and B1 are able to synthesize mycobactin. From the desferri-triscatecholates compounds **15a–c** and **17** were active on strain mc^2155 and B1, too. The iron complexes of the free hydroxamates **8d–g, 9d, e, 10d** and **11d, e** as well as the iron complexes of all triscatecholates were effective growth promotors of the wild type strain mc^2155 and the single mycobactin (M24) or exochelin (B1) mutant. All three strains provide the potential for ligand exchange with either exochelin or mycobactin to transfer iron into the mycobacterial cell. Growth promotion of mutants B3 and U3, which exclude such ligand exchange, occured by use of the iron complexes of all trishydroxamates, except the *myo*-inositol derivatives **12d, e** and the compound **9d** on U3, and by use of the glucose based triscatecholates **15a** and **15c**. These structures could be useful as shuttle vectors for antibiotic transport.

The recognition and uptake specificity of the siderophores was studied by use of selected compounds: (**9e** and **11e** as trishydroxamates, **15a–c** and **17** as triscatecholates; 2,3 dihydroxybenzoic acid (2,3-DHBA) and ferricrocin as a control (Table 3). All tested compounds promoted the growth of the wild type strains AB 2847 (TonB+), H1443 (TonB+) and

the mutant H 1875 (TonB+ and Fiu+). But not any of the compounds promoted growth of the TonB negative mutant BR 158 indicating that TonB is essential for active uptake and siderophore activity of these compounds. The trishydroxamates **9e** and **11e** and ferricrocin were active on all catecholate receptor mutants H1876, H873, H1877, H1875 confirming the siderophore activity of hydroxamates independent on FepA, Cir and Fiu. In contrast, the activity of the catecholates **15a–c** and **17** as well as of 2,3-DHBA was depending on the receptors Cir and Fiu, resulting in slightly decreased activity on the single Fiu or Cir mutants H1877 or H1875 and in complete inactivity on the Cir, Fiu double mutant H1876.

In the chromazurol-S (CAS) assay (Table 1) the compounds with free hydroxamate or catecholate groups showed positive results, but the protected hydroxamates **6–12a** and the catecholate with benzoxazine group **14** were inactive.

Examplarily for all hydroxamates and catecholates the stability constants of the iron complexes of **9e** and **15b** were determined by the group of Prof. Crumbliss, Durham, NC (Dhungana *et al.* 2001, 2002). The stability constants correspond with that of natural siderophores like ferrichrome and enterobactin and demonstrate that these compounds possess a high degree of Fe(III) binding stability.

In conclusion, new trishydroxamates, especially their iron complexes, and triscatecholates based on the monosaccharides methyl α-D-glucopyranoside, methyl α-D-galactopyranoside, methyl α-D ribopyranoside and methyl α-D-xylopyranoside, but not the inositol derivatives, can act as artificial siderophores in Gram-negative bacteria and mycobacteria. Such compounds are of interest as penetration vectors for antibiotics or for other biological applications involving the iron uptake and metabolism.

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