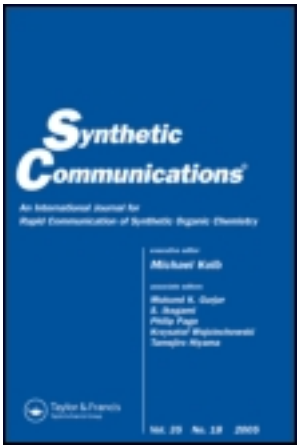

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Solvent- and Catalyst-Free Selective Mannich Reaction on Catechols and Para Substituted Phenols: A Convenient Route to Catechol- and Phenol-Iminodiacetic Acid Ligands

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Solvent- and Catalyst-Free Selective Mannich Reaction on Catechols and *Para* Substituted Phenols: A Convenient Route to Catechol- and Phenol-Iminodiacetic Acid Ligands

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ABSTRACT

We have developed a convenient solvent- and catalyst-free selective Mannich reaction of a variety of *para*-substituted phenols or catechols with paraformaldehyde and ethyl iminodiacetate. With *para*-substituted

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phenols and electron-poor catechol, only the monosubstituted benzyliminodiacetic ester is selectively formed in good yield and no disubstituted product is detected. In contrast, electron rich catechols gave mono- or disubstituted derivatives depending on the stoichiometry of ethyliminodiacetate. Furthermore, the reaction is highly regioselective with catechols, since no *para* derivatives are formed. In addition, we describe a mild acidic hydrolysis of the ester functions, which avoids the degradation of the benzylamine moiety by the quinone methide pathway. So, pure *o*-hydroxybenzyliminodiacetic acid ligands are obtained in overall good yields.

Key Words: Iminodiacetic ligands; Selective Mannich reaction; Solvent and catalyst free; *Para*-substituted phenols; Catechols.

INTRODUCTION

Catechol and phenol complexes are of great importance in bioinorganic and biomedicinal chemistry. For instance, catechol ligands have found applications as natural and artificial siderophores devoted to the supplementation of iron (III).[1–3] In another connection, a variety of compounds containing both the iminodiacetic and the phenol moieties have been studied by Maddalena et al.[4] and Awaluddin et al.[5] as potential radiopharmaceutical complexes of ^{99m}Tc. We are curently interested in the development of new radiopharmaceuticals based on ^{67}Ga nuclide with nuclear characteristics complementary to ^{99m}Tc.[6,7] So we decided to study the gallium complexes of a variety of catechols and phenols derivatized with an iminodiacetic group. Curiously, no details regarding the synthesis of most of the desired *o*-hydroxy-benzyliminodiacetic ester precursors were found in the literature survey. To achieve the preparation of those compounds, the Mannich reaction seems to be very attractive because no special equipment is required and only commercially available starting compounds are needed. As a general case, this aminomethylation reaction of aromatic compounds is performed in aqueous alcoholic solvents,[8–10] in benzene,[11] in toluene, or in a mixture of toluene-ethanol.[12] Mojtahedi et al. have already reported a solvent-free Mannich reaction on electron rich aromatic compounds, but it involves both acid (silica gel) and ultrasound activation.[13,14] The procedure described here appears to be superior to others because it is environmently friendly (solvent-free and catalyst-free), no special apparatus e.g., microwave oven is required, and it is equally efficient on electron-poor and electron-rich phenolic compounds.

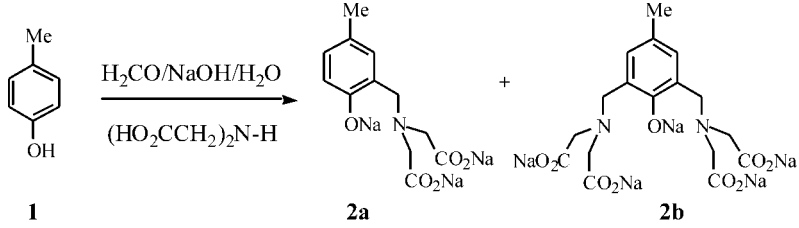
RESULTS AND DISCUSSION

a) Mannich Reaction on Phenols and Catechols

To find optimum conditions for Mannich aminomethylation, cresol **1** was chosen as a standard substrate. It was reacted in water with formaldehyde, iminodiacetic acid in strongly basic (aqueous NaOH) condition following the original method depicted by Schwarzenbach et al.[15] But, by this way it is impossible to obtain the desired monosubstituted product **2a** without the disubstituted one **2b** Eq. (1).

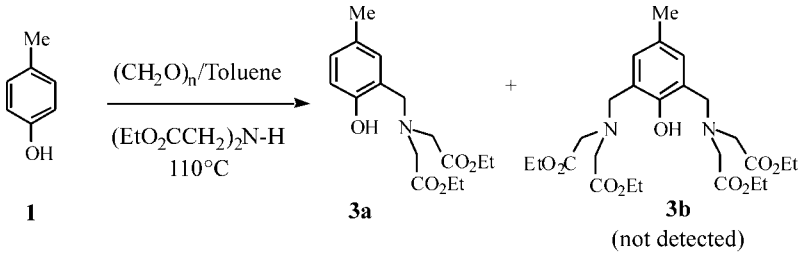
Moreover, the separation of those products (the resulting sodium salts **2a** and **2b**, or their hydrochloric salts obtained after acidification), turned out to be a difficult task. So, to avoid the tedious purification of such ionic compounds and therefore to allow a more accurate column chromatographic procedure in the separation step, the ethyl ester of iminodiacetic acid was employed. In counterpart to its hydrophobic and base sensitive nature, the ester functions imposes a nonaqueous solvent and the absence of strong base (like NaOH or KOH) during the reaction. The Mannich reaction of cresol **1** was then attempted in toluene with paraformaldehyde (in excess) as an anhydrous source of formaldehyde. If toluene proved to be a good solvent in some Mannich reactions performed at room temperature, in our case the reaction was very slow. It became only effective at reflux temperature (110°C) in 48 hours. Worthy of note, the sole product formed during this reaction is the mono *ortho*-substituted compound **3a** Eq. (2). In contrast to the Schwarzenbach conditions (aqueous NaOH),[15] the *ortho-ortho′* disubstituted compound **3b** is not detected, even if a large excess of ethyl iminodiacetate and paraformaldehyde or prolonged reaction time are used.

In order to simplify this reaction, a solvent-free reaction was attempted with three representative electron-rich or electron-deficient phenols Eq. (3) and the results compared to those obtained in toluene.



1 **2a** **2b**

Equation 1. Aminomethylation of cresol with iminodiacetic acid in basic condition.

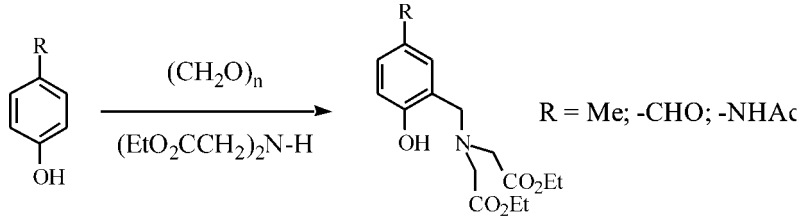


Equation 2. Aminomethylation of cresol with ethyl iminodiacetate in toluene.

It is noteworthy that the supression of the solvent did not change the selectivity of the reaction: only the monosubstituted compounds are again isolated; no disubstituted compound is detected (even with a large excess of iminodiacetate ester and paraformaldehyde). The solvent-free reaction proved to be superior because it ensures a more rapid reaction than in toluene (16 hours against 24 hours) and the temperature may be lowered from 110°C to 50°C with no detrimental effect on the yield (Table 1). Furthermore, the decrease of the temperature seems to be beneficial since an increase of the yield is noticeable, especially in the case of the derivatives **4** and **5**.

Then, this procedure was successfully applied to a variety of *para*-substituted phenols (Table 2). After purification, the products are also isolated in good yield. However, it is not possible to establish a correlation between the yield and the electron-donating or electron-withdrawing effect of the group fixed at the *para* position of the phenol.

An extension of the above procedure has also been conducted on catechol and 3,4-dihydroxybenzaldehyde, which are interesting starting compounds for the synthesis of potentialy binucleating ligands for complexation experiments. The results of Mannich reactions conducted without solvent on such catechols are summarized on Fig. 1.



Equation 3. Aminomethylation of three representative phenols in toluene or without solvent.

Table 1. Mannich reaction with or without solvent on representative phenols.

Products	Isolated yield after 24 hours in toluene (reflux, 110°C)	Isolated yield after 16 hours without solvent (50°C)
3a R = Me-	70%	76%
4 R = OHC-	58%	75%
5 R = AcNH-	29%	47%

For the catechol, the reaction is highly regioselective: only the *ortho* monosubstituted product **10a** was formed during the reaction, and no substitution occured at the *para* position. On the other hand, it was found that contrary to the results obtained with the *para*-substituted phenols, it is possible in the case of catechol to enforce the double substitution at the *ortho* and *ortho* positions (product **10b**, yield 47%) if two equivalents of ethyl iminodiacetate are involved during the reaction. It appears that the presence of a second hydroxy group on catechol enhances the reactivity of the aromatic ring.

In the case of 3,4-dihydroxybenzaldehyde, a deactivated catechol, the aminoalkylation is limited to the monosubstitution step (yield of **11a**, 60%); even though two equivalents of ethyl iminodiacetate are used or prolonged reaction time (48 hours), the disubstituted product **11b** is not observed. Here again the reaction is highly regioselective since only the *meta* (with respect to the aldehyde) regioisomer **11a** is isolated as a sole new reaction product. This structural assignment of **11a** was unequivocaly based on the observation of two distinct aromatic protons showing a typical $^4J_{H\text{-}H}$ coupling value ($^4J_{H\text{-}H} = 1.8$ Hz) in ^{1}H NMR analysis.

b) Hydrolysis of the Ester Function

The synthezised compounds possess latent carboxylic acid groups that could be simply regenerated from ester by saponification or acid hydrolysis.

Table 2. Mannich reaction without solvent with ethyl iminodiacetate and *p*-phenols at 50°C.

Product	**3a**	**4**	**5**	**6**	**7**	**8**	**9**
R=	Me	CHO	AcNH	CH_2CO_2Et	NO_2	F	MeO
Yield	76%	75%	47%	74%	74%	73%	72%

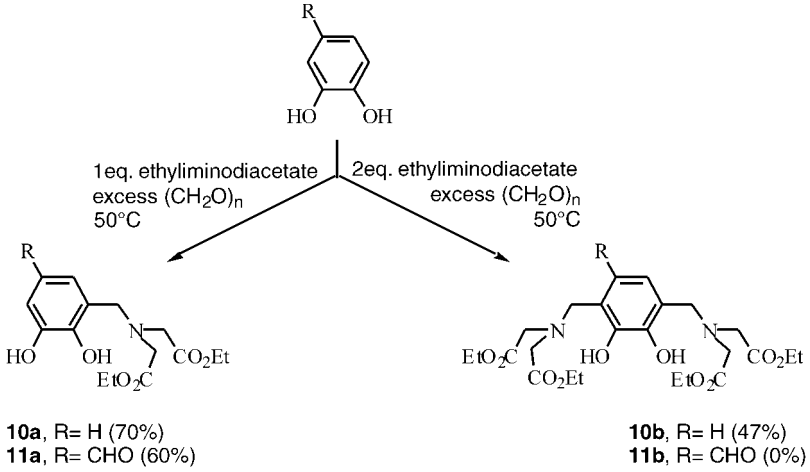
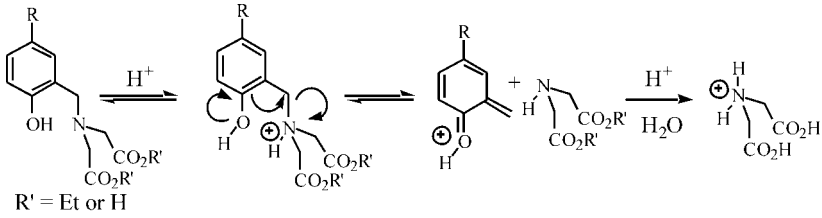


Figure 1. Mannich reaction on catechol and 3,4-dihydroxybenzaldehyde without solvent.

The former method is not advantageous since sodium or potassium salts, which are hygroscopics and difficult to purify, are obtained. Finally, we chose to remove the ester function by hydrolysis with aqueous hydrochloric acid. Preliminary results show that the treatment of the esters with hydrochloric acid at high or moderate concentration [(HCl) = 10 M to 5 M)] and at the refluxing temperature is not satisfactory because the deamination of the product was observed. Indeed, a substantial amount of iminodiacetic acid is isolated after refluxing the compounds during the time necessary to obtain a complete removing of the esters. This reactivity is very likely due to a retro-Michael reaction involving a quinone methyde intermediate Eq. (4) as reported by Tramontini and Angliolini.[16]



Equation 4. Retro-Michael activated by acidic catalysis.

To supress this side reaction, a simple decrease of the temperature from reflux to 50°C is sufficient to ensure a quantitative, clean, and smooth hydrolysis of the esters function to give the targets compounds in pure form.

In conclusion, by a simple solvent-free and catalyst-free Mannich reaction with ethyl iminodiacetate and phenols or catechols, we achieved the selective synthesis of pure esters precursors of chelating compounds in good yields. This result points out the interest of performing Mannich reactions without solvent. The subsequent hydrolysis of the esters was optimized to lead in a quantitative yield to the desired ligands. The gallium complexes of those compounds are under study.

EXPERIMENTAL

Reagents are commercially available from Aldrich and Acros companies and were used without further purification. Solvents were dried and distilled before utilization. Melting points were determined on a Büchi-Totoli capillary aparatus and were uncorrected. The NMR spectra were obtained with a Bruker Avance 300 (300 MHz for ^{1}H, 282.4 MHz for ^{19}F, and 75.5 MHz for ^{13}C) or a Bruker AM 200 (200 MHz for ^{1}H and 50 MHz for ^{13}C). The chemical shifts are reported in ppm downfield from internal Me_4Si for ^{1}H and ^{13}C ($CDCl_3$ as solvent), from internal sodium trimethylsilylpropansulfonate for ^{1}H and ^{13}C (D_2O as solvent) and from external $CFCl_3$ for ^{19}F. MS was recorded on Nermag-R10 spectometer. IR spectra were recorded (Nicolet Impact 400 apparatus) as KBr pellets for solid and as films between KBr discs for liquids. TLC was carried out on precoated Merck silica gel aluminium plates $60F_{254}$. Column chromatography was performed using silica gel 60 (230–240 mesh). The elemental analysis was carried out at the Service Central d'Analyse du CNRS (Vernaison, France).

A) Mannich Reactions on Phenols and Catechols

General Procedure I for the Mannich Reaction in Toluene

In a 50-mL flask, *p*-phenols or catechols (1 mmol), and ethyl iminodiacetate (1 mmol), and paraformalehyde (1.1 mmol) were refluxed in 10 mL of toluene under positive pressure of argon. Two additions of paraformalehyde were introduced at 12 and 36 hours in order to compensate the sublimation of paraformalehyde. After 48 hours, the toluene was evaporated and the oily residue was purified by column chromatography over silicagel to give the pure product.

General Procedure II for the Solvent-Free Mannich Reaction with Para-Substituted Phenols or Catechols

A typical procedure is as follows: *para*-substituted phenol or catechol (1 mmol), ethyl iminodiacetate (1 mmol or 2 mmol for disubstitution), and paraformaldehyde (1.1 mmol or 2.2 mmol for disubstitution) were stirred at 50°C for 16 hours under positive pressure of argon. The oily residue was then purified by column chromatography over silica gel with the appropriate eluent to give after evaporation of the solvents a microcrystalline solid (except for compounds **8**, **10b**, and **11a**, which are obtained as oils).

-[Ethoxycarbonylmethyl-(2-hydroxy-5-methyl-benzyl)-amino]-acetic acid ethyl ester 3a: Eluent CH_2Cl_2/ethyl acetate 95/5 to 90/10. Procedure I yield: 70%. Procedure II yield: 76%. Mp 65–66°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24–1.31 (t, $^3J = 7.2$ Hz, 6H), 2.23 (s, 3H), 3.52 (s, 4H), 3.94 (s, 2H), 4.15–4.25 (q, $^3J = 7.2$ Hz, 4H), 6.76 (d, $^4J = 1.7$ Hz, 1H), 6.76–6.80 (d, $^3J = 8.2$ Hz, 1H), 6.97–7.02 (dd, $^3J = 8.2$ Hz, $^4J = 1.7$ Hz, 1H), 9.5 (s, O-H, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1, 20.3, 53.8, 56.2, 61.0, 116.3, 120.9, 128.2, 129.8, 130.0, 155.1, 170.7. IR (neat, KBr): (O-H) 3265, (C-H) 2979, (C=O) 1746, (C-O) 1192 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 310 ($M + H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2 + H^+$]. Anal. calcd. for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53; O, 25.86. Found: C, 62.42; H, 7.47; N, 4.64; O, 25.74.

-[Ethoxycarbonylmethyl-(5-formyl-2-hydroxy-benzyl)-amino]-acetic acid ethyl ester 4: Eluent CH_2Cl_2/ethyl acetate 9/1. Procedure I yield: 58%. Procedure II yield: 75%. Mp: 36–37°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25–1.32 (t, $^3J = 6.9$ Hz, 6H), 3.53 (s, 4H), 4.05 (s, 2H), 4.17–4.28 (q, $^3J = 6.9$ Hz, 4H), 6.98–7.00 (d, $^3J = 8.6$ Hz, 1H), 7.57 (d, $^4J = 1.7$ Hz, 1H), 7.72–7.77 (dd, $^3J = 8.6$ Hz, $^4J = 1.7$ Hz, 1H), 9.82 (s, 1H), 10.35 (s, OH_{phenol}, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1, 53.9, 55.7, 61.3, 117.2, 121.9, 128.8, 131.2, 132.7, 163.5, 170.7, 190.6. IR (neat, KBr): (O-H) 3249, (C-H) 2987, (C=O) 1755, (C=O) 1682, (C-O) 1191 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 324 ($M + H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2 + H^+$]. Anal. calcd. for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33; O, 29.69. Found: C, 59.21; H, 6.51; N, 4.30; O, 29.54.

-[(5-Acetylamino-2-hydroxy-benzyl)-ethoxycarbonylmethyl-amino]-acetic acid ethyl ester 5: Eluent CH_2Cl_2/CH_3CN 100/0 to 70/30. Yield procedure I: 29%. Yield procedure II: 47%. Mp: 91–92°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24–1.31 (t, $^3J = 7.2$ Hz, 6H), 2.13 (s, 3H), 3.52 (s, 4H), 3.95 (s, 2H), 4.15–4.25 (q, $^3J = 7.2$ Hz, 4H), 6.80–6.85 (d, $^3J = 8.6$ Hz, 1H), 7.13–7.19 (dd, $^3J = 8.6$ Hz, $^4J = 2.7$ Hz, 1H), 7.26–7.27 (d, $^4J = 2.7$ Hz, 1H), 9.40 (s, OH_{phenol}, 1H). NMR (50.3 MHz, $CDCl_3$): δ 14.2, 24.3, 53.9, 56.3, 61.1, 116.7, 121.4, 121.8, 122.1, 129.4, 154.3, 168.0, 170.6. IR (neat, KBr):

(O-H + N-H) 3281, (C-H) 3102, (C-H) 2987, (C═O) 1739, (C═O) 1657, (C-O) 1191 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 353 ($M+H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2+H^+$]. Anal. calcd. for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86; N, 7.95; O, 27.24. Found: C, 57.26; H, 6.91; N, 7.95; O, 27.61.

-{3-[(Bis-ethoxycarbonylmethyl-amino)-methyl]-4-hydroxy-phenyl}-acetic acid ethyl ester 6: Eluent CH_2Cl_2/ethyl acetate 8/2. Procedure II yield: 77%. Mp: 48–49°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24–1.32 (t, $^3J=7.2$ Hz, 6H), 1.58–1.61 (t, $^3J=6.2$ Hz, 1H, OH), 3.53 (s, 4H), 3.98 (s, 2H), 4.15–4.26 (q, $^3J=7.2$ Hz, 4H), 4.55–4.58 (d, $^3J=6.2$ Hz, 2H), 6.85–6.89 (d, $^3J=8.2$ Hz, 1H), 6.99–7.00 (d, $^4J=2.1$ Hz, 1H), 7.17–7.21 (dd, $^3J=8.2$ Hz, $^4J=2.1$ Hz, 1H), 9.44 (s, OH_{phenol}, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1, 53.9, 56.2, 61.1, 65.1, 116.7, 121.3, 128.7, 128.8, 131.7, 157.2, 170.7. IR (neat, KBr): (O-H) 3355, (C-H) 2987, (C═O) 1739, (C-O) 1192 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 326 ($M+H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2+H^+$]. Anal.calcd. for $C_{16}H_{23}NO_6$: C, 59.06; H = 7.13; N = 4.31; O = 29.50. Found: C, 58.97; H, 7.23; N, 4.53; O, 29.53.

-[Ethoxycarbonylmethyl-(2-hydroxy-5-nitro-benzyl)-amino]-acetic acid ethyl ester 7: Eluent CH_2Cl_2. Procedure II yield 74%. Mp: 75°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.29 (t, $^3J=7.0$ Hz, 6H), 3.51 (s, 4H), 4.02 (s, 2H), 4.16–4.24 (q, $^3J=7.0$ Hz, 4H), 6.89–6.93 (d, $^3J=9.0$ Hz, 1H), 7.92–7.93 (d, $^4J=2.7$ Hz, 1H), 8.07–8.11 (dd, $^3J=9.0$ Hz, $^4J=2.7$ Hz, 1H), 10.49 (s, OH_{phenol}, 1H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 14.0, 53.9, 55.4, 61.3, 117.0, 121.6, 125.7, 125.8, 140.1, 163.6, 170.6. IR (neat, KBr): (O-H) 3200, (C-H) 3040, (C-H) 2980, (C═O) 1715, (N-O) 780 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 341 ($M+H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2+H^+$]. Anal. calcd. for $C_{15}H_{20}N_2O_7$: C, 52.94; H = 5.92; N = 8.23; O = 32.91. Found: C, 53.35; H, 5.89; N, 8.64; O, 32.54%.

-[Ethoxycarbonylmethyl-(5-fluoro-2-hydroxy-benzyl)-amino]-acetic acid ethyl ester 8: Eluent CH_2Cl_2/ethyl acetate 95/5. Procedure II yield: 73% (oil). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.30 (t, $^3J=7.2$ Hz, 6H), 3.51 (s, 4H), 3.94 (s, 2H), 4.19–4.23 (q, $^3J=7.2$ Hz, 4H), 6.67–6.71 (dd, $^3J=8.7$ Hz, $^4J=2.9$ Hz, 1H), 6.78–6.85 (m, 1H), 6.86–6.92 (m, 1H), 9.10 (s, OH_{phenol}, 1H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 14.1, 53.8, 55.8, 61.1, 115.4, 115.6, 115.8, 115.9, 117.3 et 117.4, 153.43–153.41 (C-F), 157.5, 170.7. ^{19}F RMN (282.39 MHz, $CDCl_3$): δ − 126.32. IR (neat, KBr): (O-H) 3346, (C-H) 2987, (C═O) 1739, (C-O) 1200, (C-F) 1020 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 314 ($M+H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2+H^+$]. Anal. calcd. for $C_{15}H_{20}NO_5F$: C, 57.50; H, 6.43; N, 4.47. Found: C, 57.58; H, 6.45; N, 4.42.

-[Ethoxycarbonylmethyl-(2-hydroxy-5-methoxy-benzyl)-amino]-acetic acid ethyl ester 9: Eluent CH_2Cl_2/ethyl acetate 8/2. Procedure II yield: 72%. Mp: 76°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.30 (t, $^3J=7.2$ Hz, 6H), 3.52 (s, 4H), 3.72 (s, 3H), 3.94 (s, 2H), 4.16–4.23 (q, $^3J=7.2$ Hz,

4H), 6.54–6.55 (d, $^4J = 2.7$ Hz, 1H), 6.73–6.83 (m, 2H), 8.93 (s, OH_{phenol}, 1H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 14.5, 53.8, 55.7, 56.3, 61.0, 114.3, 115.3, 117.0, 121.9, 151.3, 152.5, 170.7. MS (CI, NH_3 + *iso*butane) m/z: 326 ($M + H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2 + H^+$]. Anal. calcd. for $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 58.8; H, 7.16; N, 4.20.

-[(2,3-Dihydroxy-benzyl)-ethoxycarbonylmethyl-amino]-acetic acid ethyl ester 10a: Eluent CH_2Cl_2/ethyl acetate 95/5 to 90/10. Procedure I yield: 54%. Procedure II yield: 70%. Mp: 39–40°C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26–1.30 (t, $^3J = 7.2$ Hz, 6H), 3.52 (s, 4H), 3.95 (s, 2H), 4.17–4.25 (q, $^3J = 7.2$ Hz, 4H), 5.67 (s, $H_{catechol}$, 1H), 6.50–6.53 (dd, $^3J = 7.6$ Hz, $^4J = 1.6$ Hz, 1H), 6.67–6.72 (m, $^3J = 7.6$ Hz, $^4J = 7.6$ Hz, 1H), 6.86–6.89 (dd, $^3J = 7.6$ Hz, $^4J = 1.6$ Hz, 1H), 9.68 (s, $OH_{catechol}$, 1H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 14.1, 54.0, 56.0, 61.2, 114.5, 119.6, 120.5, 121.4, 143.9, 145.1, 171.0. IR (neat, KBr): (O-H) 3500–3200, (C-H) 3061, (C-H) 2979, (C=O) 1730, (C-O) 1200 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 312 ($M + H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2 + H^+$]. Anal. calcd. for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.94; H, 6.88; N = 4.62.

-({4-[(Bis-ethoxycarbonylmethyl-amino)-methyl]-2,3-dihydroxy-benzyl}-ethoxycarbonylmethyl-amino)-acetic acid ethyl ester 10b: Eluent CH_2Cl_2/ethyl acetate 95/5 to 90/10. Procedure I yield: 44%. Procedure II yield: 47% (oil). ^1H NMR (200 MHz, $CDCl_3$): δ 1.20–1.31 (t, $^3J = 7.2$ Hz, 12H), 3.54 (s, 8H), 3.96 (s, H), 4.14–4.25 (q, $^3J = 7.2$ Hz, 8H), 6.48 (s, 2H), 8.85 (s, $OH_{catechol}$, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1, 53.9, 55.5, 60.9, 119.8, 121.9, 145.2, 170.7. IR (neat, KBr): (O-H) 3363, (C-H) 2979, (C=O) 1730, (C-O) 1200 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 513 ($M + H^+$), 324 [$M + H^+$-$HN(CH_2CO_2Et)_2$], 190 [$HN(CH_2CO_2Et)_2 + H^+$]. Anal. calcd. for $C_{15}H_{21}NO_6$: C, 56.24; H, 7.08; N = 5.47. Found: C, 55.86; H, 7.09; N, 5.52.

-[Ethoxycarbonylmethyl-(5-Formyl-2,3-dihydroxy-benzyl)-amino]-acetic acid ethyl ester 11a: Eluent CH_2Cl_2/ethyl acetate 95/5 to 90/10. Procedure II yield 59% (oil). ^1H NMR (200 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.40 (d, $^4J = 1.8$ Hz, 1H), 7.15 (d, $^4J = 1.8$ Hz, 1H), 4.23 (q, $^3J = 6.8$ Hz, 4H), 4.03 (s, 2H), 3.53 (s, 4H), 1.29 (t, $^3J = 7.18$ Hz, 6H). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 14.1, 53.9, 55.6, 61.4, 115.4, 121.5, 123.5, 129.0, 145.5, 150.0, 170.9, 190.8. MS (CI, NH_3 + *iso*butane) m/z: 340 ($M + H^+$, 100%), 190 [$HN(CH_2CO_2Et)_2 + H^+$]. Anal. calcd. for $C_{16}H_{21}O_7N$: C, 56.63; H, 6.19; N, 4.13; O, 33.04. Found: C, 56.64; H, 6.17; N, 4.18; O, 32.63.

B) Hydrolysis of the Ester Functions

General procedure: the appropriate ester (1 mmol) was dissolved in 10 M HCl (50 mL). The mixture was heated overnight at 50°C. After cooling, the

water was evaporated under reduced pressure to give the pure acid, which was isolated in quantitative yield as the hydrochloric salt (hygroscopic).

-[Carboxymethyl-(2-hydroxy-5-methyl-benzyl)-amino]-acetic acid: from hydrolysis of **3a**. ^{1}H NMR (200 MHz, D_2O, pD = 1.6): δ 2.08 (s, 3H), 3.94 (s, 4H), 4.36 (s, 2H), 6.70–6.72 (d, $^{3}J = 8.2$ Hz, 1H), 7.00 (d, $^{4}J = 1.8$ Hz, 1H), 7.04–7.07 (dd, $^{3}J = 8.2$ Hz, $^{4}J = 1.8$ Hz, 1H). ^{13}C NMR (50.31 MHz, D_2O, pD = 1.6): δ 19.7, 54.7, 55.4, 114.9, 116.2, 131.0, 133, 133.7, 153.7, 169.0. IR (KBr disc): (O-H) 3281, (C-H_{ar}) 3077, (C-H_{ar}) 3012, (C-H) 2963, (C=O) 1722 cm^{-1}. MS (FAB^{+}, glycerol matrix) m/z: 254 (M + H^{+}, 100%).

Anal. calcd. for $C_{12}H_{15}NO_5$, HCl, 0.5 H_2O: C, 48.24; H, 5.69; N, 4.69. Found: C, 48.6; H, 5.89; N = 4.82.

-[Carboxymethyl-(5-formyl-2-hydroxy-benzyl)-amino]-acetic acid: from hydrolysis of **4**. ^{1}H NMR (200 MHz, D_2O, pD = 11.0): δ 3.15 (s, 4H), 3.61 (s, 2H), 6.60–6.64 (d, $^{3}J = 8.6$ Hz, 1H), 7.63–7.68 (dd, $^{3}J = 8.6$ Hz, $^{4}J = 2.3$ Hz, 1H), 7.79–7.80 (d, $^{4}J = 1.7$ Hz, 1H), 9.39 (s, 1H). ^{13}C NMR (75.46 MHz, D_2O, pD = 11.0): δ 56.2, 56.7, 123.1, 124.3, 130.4, 135, 138, 182.6, 195.8. IR (KBr disc): (O-H) 3306, (C-H_{ar}) 3020, (C-H) 2955, (C=O) 1690, (C=O) 1608 cm^{-1}. MS (CI, NH_3 + *iso*butane) m/z: 268 (M + H^{+}). Anal. Calcd. for $C_{12}H_{13}NO_6$, HCl, 1 H_2O: C, 44.79; H, 4.97; N, 4.35. Found: C, 44.80; H, 4.82; N, 4.3.

-[(5-Amino-2-hydroxy-benzyl)-carboxymethyl-amino]-acetic acid: from hydrolysis of **5**. ^{1}H NMR (300 MHz, D_2O, pD = 1.5): δ 4.15 (s, 4H), 4.64 (s, 2H), 7.09–7.13 (dd, $^{3}J = 8.3$ Hz, $^{4}J = 1$ Hz, 1H), 7.40–7.44 (d, $^{3}J = 8.3$ Hz, 1H), 7.44 (d, $^{4}J = 1$ Hz, 1H). ^{13}C NMR (50.3 MHz, D_2O, pD = 1.5): δ 54.8, 55.2, 116.9, 117.6, 122.4, 127.5, 127.9, 156.9, 169.1. MS (IC, NH_3 + *iso*butane) m/z: 255 (M + H^{+}, 100%). IR (KBr disc): (O-H + N-H) 3400–3200, (C-H_{ar}) 3020, (C-H) 2955, (C=O) 1755 cm^{-1}. Anal. Calcd. for $C_{11}H_{14}N_2O_5$, 2HCl, 1.5 H_2O: C,37.30; H, 5.41; N, 7.91. Found: C, 37.45; H, 5.27; N = 7.83.

-{3-[(Bis-carboxymethyl-amino)-methyl] − 4-hydroxy-phenyl}-acetic acid: from hydrolysis of **6**. ^{1}H NMR (300 MHz, D_2O, pD = 1.4): δ 3.70 (s, 2H), 4.18 (s, 4H), 4.60 (s, 2H), 6.97–7.00 (d, $^{3}J = 8.3$ Hz, 1H), 7.28 (d, $^{2}J = 2.2$ Hz, 1H), 7.28–7.34 (dd, $^{3}J = 8.3$ Hz, $^{2}J = 2.2$ Hz, 1H). ^{13}C NMR (50.3 MHz, D_2O, pD = 1.4): δ 39.6, 54.5, 55.2, 115.3, 116.5, 126.7, 133.8, 134.5, 155.4, 168.8, 177.1. IR (KBr disc): (O-H) 3400–3000, (C=O) 1738, (C-O) 1200 cm^{-1}. MS (FAB^{+}, glycerol matrix) m/z: 298 (M + H^{+}, 100%). Anal. Calcd. for $C_{13}H_{15}NO_7$, HCl, 1.5 H_2O: C, 43.27; H, 5.27; N, 3.88. Found: C, 43.36; H, 5.20; N, 3.89.

-[Carboxymethyl-(2-hydroxy-5-nitro-benzyl)-amino]-acetic acid: from hydrolysis of **7**. ^{1}H NMR (300 MHz, D_2O, pD = 12): δ 3.00 (s, 4H), 3.42 (s, 2H), 6.32–6.35 (d, $^{3}J = 9.2$ Hz, 1H), 7.83–7.87 (d, $^{3}J = 9.2$ Hz,

$^2J = 3.1$ Hz, 1H), 8.03–8.04 (d, $^2J = 3.1$ Hz, 1H). ^{13}C NMR (50.3 MHz, D_2O, pD = 12): δ 54.7, 59.1, 119.7, 127.5, 127.8, 129.2, 133.1, 180.2. IR (KBr disc): (O-H) 3400–3000, (CH) 2996, (CO) 1738 cm^{-1}. MS (FAB$^+$, glycerol matrix) m/z: 284 ($M + H^+$, 100%), 282 (M-H$^+$). Anal. Calcd. for $C_{11}H_{12}N_2O_7$, HCl, 0.5 H_2O: C, 39.63; H, 4.32; N, 8.40. Found: C, 39.67; H, 4.57; N, 8.17.

-[Carboxymethyl-(5-fluoro-2-hydroxy-benzyl)-amino]-acetic acid: from hydrolysis of **8**. ^{1}H NMR (300 MHz, D_2O, pD = 11): δ 3.18 (s, 4H), 3.60 (s, 2H), 6.54–6.58 (m, 1H), 6.80–6.6.87 (m, 1H), 7.07–7.12 (m, 1H). ^{13}C NMR (75.4 MHz, D_2O, pD = 11): δ 55.7, 57.7, 115.5–115.8 ($J_{C\text{-}F} = 23$ Hz), 116.8–117.2 ($J_{C\text{-}F} = 29$ Hz), 117.1 ($J_{C\text{-}F} = 7.3$ Hz), 124.5–124.6 ($J_{C\text{-}F} = 7$ Hz), 153.3, 154.6–157.7 ($J_{C\text{-}F} = 234$ Hz), 178.9. ^{19}F NMR (282.39 MHz, D_2O): δ 132.05. IR (KBr disc): (O-H) 3400–3000, (C=O) 1738 cm^{-1}. MS (FAB$^+$, glycerol matrix) m/z: 258 ($M + H^+$). Anal. Calcd. for $C_{11}H_{12}NO_5F$, HCl, 0.5 H_2O: C, 43.63; H, 4.63; N, 4.63. Found: C, 43.88; H, 4.58; N = 4.51.

-[Carboxymethyl-(2-hydroxy-5-methoxy-benzyl)-amino]-acetic acid: from hydrolysis of **9**. ^{1}H NMR (300 MHz, D_2O, pD = 12): δ 3.15 (s, 4H), 3.58 (s, 2H), 3.76 (s, 3H), 6.55–6.58 (d, $^3J = 8.7$ Hz, 1H), 6.73–6.77 (dd, $^3J = 8.7$ Hz, $^2J = 3.4$ Hz, 1H), 6.97–6.98 (d, $^2J = 3.4$ Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O, pD = 12): δ 54.8, 57.0, 59.0, 115.1, 117.2, 119.1, 127.3, 148.0, 160.3, 180.5. IR (KBr disc): (O-H) 3224, (C-H_{ar}) 3061, (CH) 2990, (C=O) 1747 cm^{-1}. MS (FAB$^+$, glycérol matrix) m/z: 270 ($M + H^+$), 137 ([$M + H^+$-HN(CH_2CO_2H)$_2$], 100%), 134 [HN(CH_2CO_2H)$_2 + H^+$]. Anal. Calcd. for $C_{12}H_{15}NO_6$, HCl, 1.5 H_2O: C, 43.32; H, 5.47; N, 4.21. Found: C, 43.71; H, 5.65; N = 4.35.

-[Carboxymethyl-(2,3-dihydroxy-benzyl)-amino]-acetic acid: from hydrolysis **10a**. ^{1}H NMR (300 MHz, D_2O, pD = 1.9): δ 33.95 (s, 4H), 4.41 (s, 2H), 6.67–6.76 (m, 2H), 6.85–6.88 (dd, $^3J = 7.5$ Hz, $^2J = 2.2$ Hz, 1H). ^{13}C NMR (75.4 MHz, D_2O, pD = 1.9): δ 54.7, 55.1, 116.2, 118.6, 121.3, 124.6, 144.8, 145.1, 169.0. IR (KBr disc): (O-H) 3265, (C-H_{ar}) 3060, (CH) 2950, (C=O) 1746 cm^{-1}. MS (FAB$^+$, glycerol matrix) m/z: 256 ($M + H^+$, 100%). Anal. Calcd. for $C_{11}H_{13}NO_6$, HCl: C, 45.29; H, 4.84; N, 4.80. Found: C, 44.92; H, 5.18; N, 4.71.

-({4-[(Bis-carboxymethyl-amino)-methyl]-2,3-dihydroxy-benzyl}-carboxymethyl-amino)-acetic acid: from hydrolysis of **10b**. ^{1}H NMR (300 MHz, D_2O, pD = 1.9): δ 3.87 (s, 8H), 4.41 (s, 4H), 6.85 (s, 2H). ^{13}C NMR (75.4 MHz, D_2O, pD = 1.9): δ 55.1, 56.8, 120.5, 123.8, 146.1, 171.6. IR (KBr disc): (O-H) 3436, (CH_{ar}) 3055, (C-H) 2995, (C=O) 1738 cm^{-1}. MS (FAB$^+$, glycerol matrix) m/z: 401 ($M + H^+$, 100%). Anal. Calcd. for $C_{16}H_{20}N_2O_{10}$, 2 HCl, 1 H_2O: C, 39.12; H, 4.92; N, 5.70. Found: C, 38.96; H, 4.90; N, 5.60.

-[Carboxymethyl-(5-formyl-2,3-dihydroxy-benzyl)-amino]-acetic acid: from hydrolysis of **11a**. ^{1}H NMR (300 MHz, D_2O, pD = 1.9): δ 9.50 (s, 1 H); 7.32 (dd, $^{4}J = 1.8$ Hz, 2H); 4.49 (s, 2H); 3.99 (s, 4H). ^{13}C NMR (75.4 MHz, D_2O, pD = 1.9): δ 194.5, 168.6, 152.5, 145.4, 129.0, 115.9, 129.58, 117.1, 54.6, 54.2. IR (KBr disc): (OH) 3355, (CH_{ar}) 3120, (CH) 2990, (CO) 1746 cm^{-1}. MS (FAB^+, glycerol matrix) m/z: 284 ($M + H^+$, 100%). Anal. Calcd. for $C_{12}H_{13}NO_7$, 1HCl: C, 45.08; H, 4.41; N, 4.38. Found: C, 44.71; H, 4.70; N, 4.29.

REFERENCES

1. Neilands, J.B. Siderophores: structure and function of microbial iron transport compounds. J. Biol. Chem. **1995**, *45*, 26723–26726.
2. Thomas, F.; Beguin, C.; Pierre, J.-P.; Serratrice, G. Thermodynamic and kinetic studies of the sulfonated derivative of the iron chelator TRENCAM, an analog of enterobactin. Inorganica Chimica Acta **1999**, *291* (1–2), 148–157.
3. Serratrice, G.; Biasso, F.; Thomas, F.; Beguin, C. Mechanism of the stepwise dissociation of the Fe(III) complexes with tripodal ligands as siderophore models. Eur. J. Inorg. Chem. **2004**, *7*, 1552–1565.
4. Maddalena, D.J.; Snowdon, G.M.; Wilson, J.G. Structure-distribution studies on some ^{99m}Tc-*o*-hydroxybenzyliminodiacetic acid complexes. Nuclear Medicine and Biology **1988**, *15*, 319–325.
5. Awaluddin, A.B.; Jacobs, J.J.; Bourne, D.W.A.; Maddalena, D.J.; Wilson, J.G.; Boyd, R.E. Synthesis and characterization of potential tumor scintigraphic agents. Appl. Radiat. Isot. **1987**, *38*, 671–674.
6. Jarjayes, O.; du Moulinet d'Hardemare, A.; Averbuch-Pouchot, M.-T.; Durif, A. A μ-phenoxo-bridged digallium (III) complex with 2,6-[[*N*, *N*′bis(carboxymethyl-amino)]-methyl]-4-methylphenol dinucleating ligand. Acta Cristallographica **1998**, *C54*, 931–933.
7. Figuet, M.; Averbuch-Pouchot, M.-T.; du Moulinet d'Hardemare, A.; Jarjayes, O. Tripodal iminophenolate ligand complexes of group 13 metal ions. Eur. J. Inorg. Chem. **2001**, *8*, 2089–2096.
8. Sakiyama, H.; Mochizuki, R.; Sugawara, A.; Sakamoto, M.; Nishida, Y.; Yamasaki, M. Dinuclear zinc(II) complex of new acyclic phenol-based dinucleating ligand with four methoxyethyl chelating arms: first dizinc model with aminopeptidase function. J. Chem. Soc., Dalton Trans. **1999**, *6*, 997–1000.
9. Wilson, J.G.; Katsifis, G. Phenolic analogues of amino carboxylic acid ligands for ^{99m}Tc. Part. V. *N*-benzyl-2-(2-hydroxyphenyl)glycines

(bhpg) and *N*-benzyl-2-(4-hydroxyphenyl)-glycines (*iso*bhpg). Aust. J. Chem. **2000**, *53*, 583–587.
10. Sinhababu, A.K.; Borchardt, R.T. Selective ring *C*-methylation of hydroxybenzaldehydes *via* their Mannich bases. Synth. Commun. **1983**, *13*, 677–683.
11. Chi, K.-W.; Wei, H.-C.; Kottke, T.; Lagow, R.J. A new one-pot synthesis of double-armed ionizable crown ethers using the Mannich reaction. J. Org. Chem. **1996**, *61*, 5684–5685.
12. Bordunov, A.V.; Bradshaw, J.S.; Pastushok, V.N.; Izatt, R.M. Application of the Mannich reaction for the synthesis of azamacrocycles. Synlett **1996**, *10*, 933–948.
13. Mojtahedi, M.M.; Sharifi, A.; Mohsenzadeh, F.; Said, M. Microwave-assisted aminomethylation of electron-rich compounds under solvent-free condition. Synth. Commun. **2000**, *30*, 69–72.
14. Sharifi, A.; Mizraei, M.; Naimi-Jamal, M.R. Solvent-free aminoalkylation of phenols and indoles assisted by microwave irradiation. Monats. Chem. **2001**, *132*, 875–880.
15. Schwarzenbach, G.; Anderegg, G.; Sallmann, R. Der phenolatsauerstoff als koordinationspartner. Helv. Chim. Acta **1952**, *225*, 1785–1793.
16. Tramontini, M.; Angliolini, L. Further advance in the chemistry of Mannich bases. Tetrahedron **1990**, *46*, 1791–1837. And cited references.

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