Synthetic Approaches for Iron Type Chelators

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Abstract: Synthetic iron chelators (siderophores mimics) are of paramount interest as clinical iron removal agents (iron overload is one of the most common poisoning) and water-soluble iron complexes can be used to alleviate iron deficiency in plants. Moreover, some additional properties may be needed for a precise function (as examples, probes for studying metal transport, diagnostic tools, agent suited for vectorisation...). We describe in this review the organic syntheses of selected typical examples from our own works. (i) Amphiphilic chelators based on catechol groups. (ii) Mixed ligands based on catechol and quinoline groups. (iii) Quinolobactin, a natural siderophore. (iv) Oxinobactin, a biomimetic synthetic analog of enterobactin involving 8-hydroxyquinoline chelating subunits.

Keywords: Siderophore, catechol, 8-hydroxyquinoline, amphiphiles, tripodal scaffolds, Enterobactin.

INTRODUCTION

Iron fulfills a vital role in virtually all living organisms [1] (the only organisms which do not require iron are the well-studied genus *Lactobacillus* and some strains of *Bacillus* and *Borellia*). Among the significant roles of iron in biology are the transport, storage and activation of molecular oxygen, reduction of ribonucleotides and dinitrogen, activation and decomposition of peroxides and electron transport *via* a wide variety of electron carriers. By far, the most common mechanism of iron acquisition by microorganisms involves the chelation of ferric iron by siderophores which are low molecular weight, ferric ion specific, chelating agents elaborated by bacteria and fungi growing under low iron stress [2]. Interest in synthetic siderophores includes their potential application as clinical iron removal agents (iron overload is one of the most common poisoning) and water-soluble iron complexes can be used to alleviate iron deficiency in plants, preventing and even reversing iron chlorosis. Some additional properties may be needed for a precise function (as examples, probes for studying metal transport, diagnostic tools, agent suited for vectorisation...). These properties concern the second coordination sphere i.e. the groups that are not directly involved in the chelation but which are necessary to lead to more sophisticated chelating agents. The design of such ligands needs a rational approach for the understanding of the metal ion complexing abilities. One of the most important criteria is the efficiency of the complexing agent evidenced by the pFe^{III} values [3], calculated for $[Fe(III)]_{tot}$ = 1 mM and $[L]_{tot}$ = 10mM at pH =7.4, which provides a direct comparison of the efficiencies of the ligands for Fe^{3+}. The octahedral arrangement of donor atoms is the most favorable geometry, permitting the maximum possible distance between their formal or partial negative charges. It is generally assumed that hexadentate ligands, usually of the *tris* bidentate type allowing preorganization of the coordination sphere, are well-suited to obtain high pFe values (the problem of ligand denticity i.e. bidentate *vs.* tridentate *vs.* hexadentate ligands has already been discussed by Hider [4]). Hexadentate ligands are not easily obtained because polyamines which constitute the backbone of the ligand are well known for the difficulty and the lack of generality of the synthetic pathways. Beside the structure of the ligand, the nature of the donor atom is also an important factor. The ferric ion is a hard acid and consequently is bound more strongly by hard bases like oxygen, or nitrogen atoms in a lesser extends. So, natural siderophores and most of their synthetic models contain three catecholate or hydroxamate groups, giving stable Fe(III) octahedral complexes. Nevertheless, efficient chelators have been developed, involving other chelating subunits [5]. Those groups present specific reactivity to be taken in account during the synthesis. Several reviews have described synthetic chelators and one or the over of the biological and/or medicinal applications [6-14]. In this mini-review we briefly described only organic syntheses of recent and representative examples of new iron chelators that can find other applications with many other metals.

1. SYNTHESIS OF AMPHIPHILIC IRON CHELATORS BASED ON CATECHOL GROUPS

The synthesis of amphiphilic chelators illustrates the derivatization of the "second sphere of coordination". The starting compound is 2,3-dimethoxybenzoic acid in which the carboxylic acid could be easily derivatized to amide. Here, amphiphilic properties are introduced by the presence of a long alkyl chain linked *via* the amide bond. Amphiphilic property is important because among the mechanisms proposed for iron solubilization and transport into the cells [15], the self-assembling of amphiphilic siderophores from marine bacteria described by A. Butler *et al.* [16] exemplify a noteworthy process. These siderophores (marinobactins and aquachelins) involving hydrophilic polar peptidic head-groups and hydrophobic fatty acid tails are surface-active amphiphiles that form self-assembled structures. The bioinspired use of this strategy might resolve the crucial problem of the hydrophilic/lipophilic balance encountered with abiotic siderophores designed for iron nutrition. Amphiphilic iron chelators could also offer a new approach in iron chelation therapy. To this end, three synthetic amphiphilic catechol-based chelators (see Fig. (**1**)) have been synthesized: (**4a** = $\mathbf{L^a}$) and (**4b** = $\mathbf{L^b}$) are bidentate ligands with different chain length (C_{12} and C_{16} respectively) and ($\mathbf{L^T}$) is a *tris*-bidentate ligand with a C_{16} length chain [17].

The two monopodal ligands ($\mathbf{L^a}$) and ($\mathbf{L^b}$) were synthesized in high yield from reaction of 2,3-dimethoxybenzoyl chloride (**2**) with dodecylamine (R = Me-$(CH_2)_{11}$-) and octylamine (R = Me-$(CH_2)_8$-) respectively, followed by a deprotection step of the catechol using BBr_3 in CH_2Cl_2 (see Scheme **1**).

The tripodal ligand (**16**) = ($\mathbf{L^T}$) was obtained similarly but starting from the original scaffold 2,2,2-*tris*-[3-aminopropyl]-ethanol (**11**) previously described [18]. We have selected the architecture of the scaffold (**7**) because it perfectly mimics the preorganization of the usual tripodal commercial spacer triethylenetetramine (Tren) but offer the great advantage to allow functionalisation at the C or O pivotal atom (Fig. (**2**)). It must be noticed that C-functionalisation involving SN reactions implies neopentilic reactivity with harsh conditions and rearrangement products, so we have preferred oxidation reactions which could be realized in milder conditions without rearrangement by-products.

Recently, Madder *et al.* have also shown that despite the flexibility of the scaffold, the arms are organized in a parallel way providing a very good preorganization [19]. The synthesis is depicted

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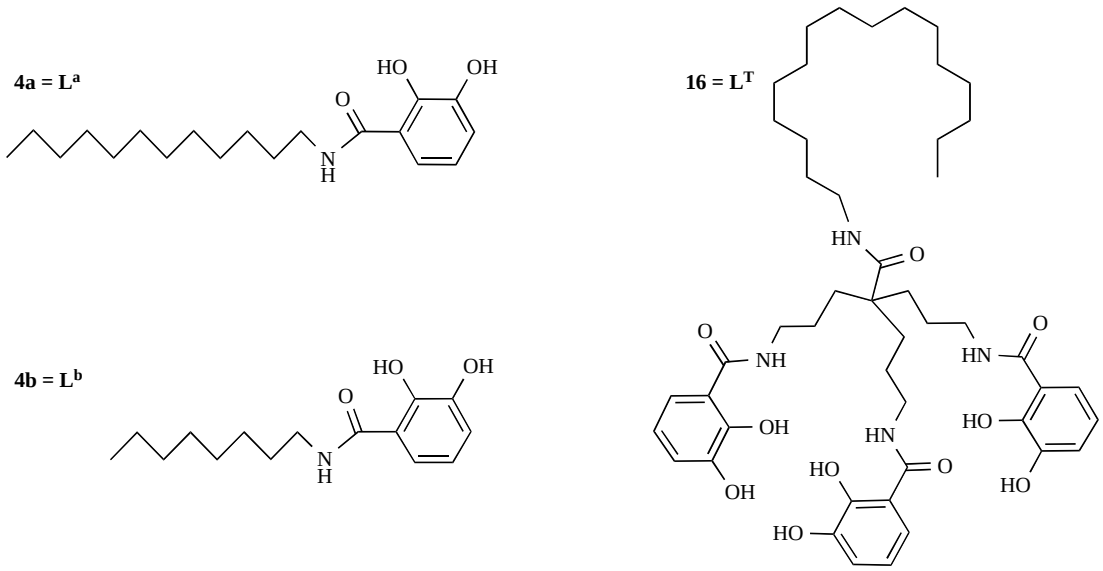
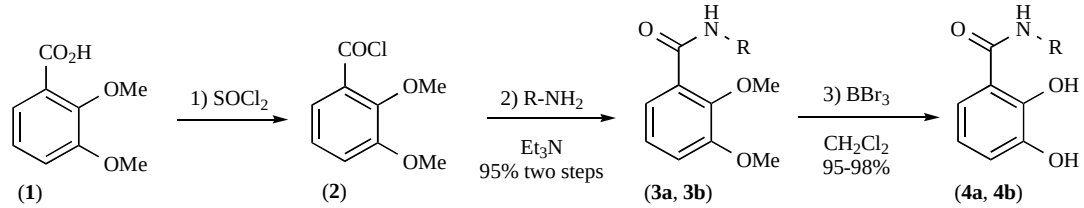


Fig. (1). Amphiphilic chelators (**4a**) = ($\mathbf{L}^{a}$), (**4b**) = ($\mathbf{L}^{b}$) and (**16**) = ($\mathbf{L}^{T}$).



Scheme 1. Synthesis of monopodal amphiphilic ligands (**4a**) = ($\mathbf{L}^{a}$) and (**4b**) = ($\mathbf{L}^{b}$).

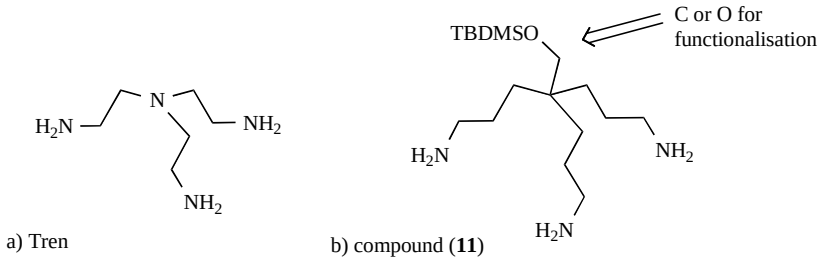


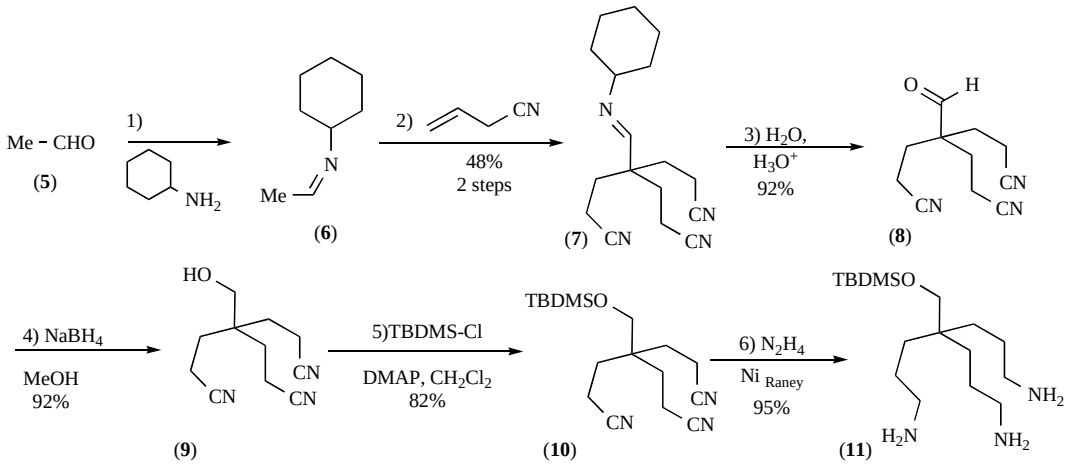
Fig. (2). a) Tren and **b)** our tripodal scaffold (**11**).

in Scheme **2**. Starting from ethanal (**5**), it is necessary to convert the aldehyde group into imine (**6**) because the latter *via* its enamine tautomeric form, is more nucleophilic for the 1,4 addition reaction of acrylonitrile than the enolic form of aldehyde. The trinitrile imine (**7**) was then back converted to aldehyde which was then reduced in alcohol (**8**) because the –CHO group will not be compatible with the primary amine (*vide infra*). Furthermore the alcohol function of the intermediate (**9**) was derivatized with a tertbutyldimethylsilyl group in order to obtain a less hydrophilic trisamine (**11**) more convenient to extract and to purify. The reduction of nitrile (**10**) to amine (**11**) with hydrides proved to be a very difficult task: $LiAlH_4$ (alone or with $AlCl_3$) [20], BH_3/THF [21], BH_3/SMe_2 [22] or $NaBH_4$ following the conditions of Osby *et al.* [23], produce a mixture of uncompleted reduced compounds which couldn't be purified. Catalytic reduction with H_2 under pressure other Raney-Ni was tried in the presence of ammonia in order to repress the deamination side reaction which could occur at the imine intermediate stage. In contrary to the previous conditions, the reduction of nitrile (**10**) was total but the triamine (**11**) was obtained in low yield (30 to 40%). Finally, the reduction was best performed at atmospheric pressure with diimide generated *in situ* by hydrazine in excess, other Raney-Ni and with KOH (those conditions avoid deamination byproducts): a very satisfactory yield of 95% of nearly pure (**11**) was obtained (it is necessary to reload periodically with N_2H_4 several time to ensure a complete reduction of the trinitrile (since the decomposition of hydrazine on Raney-Ni is faster than the complete reduction of the nitrile).

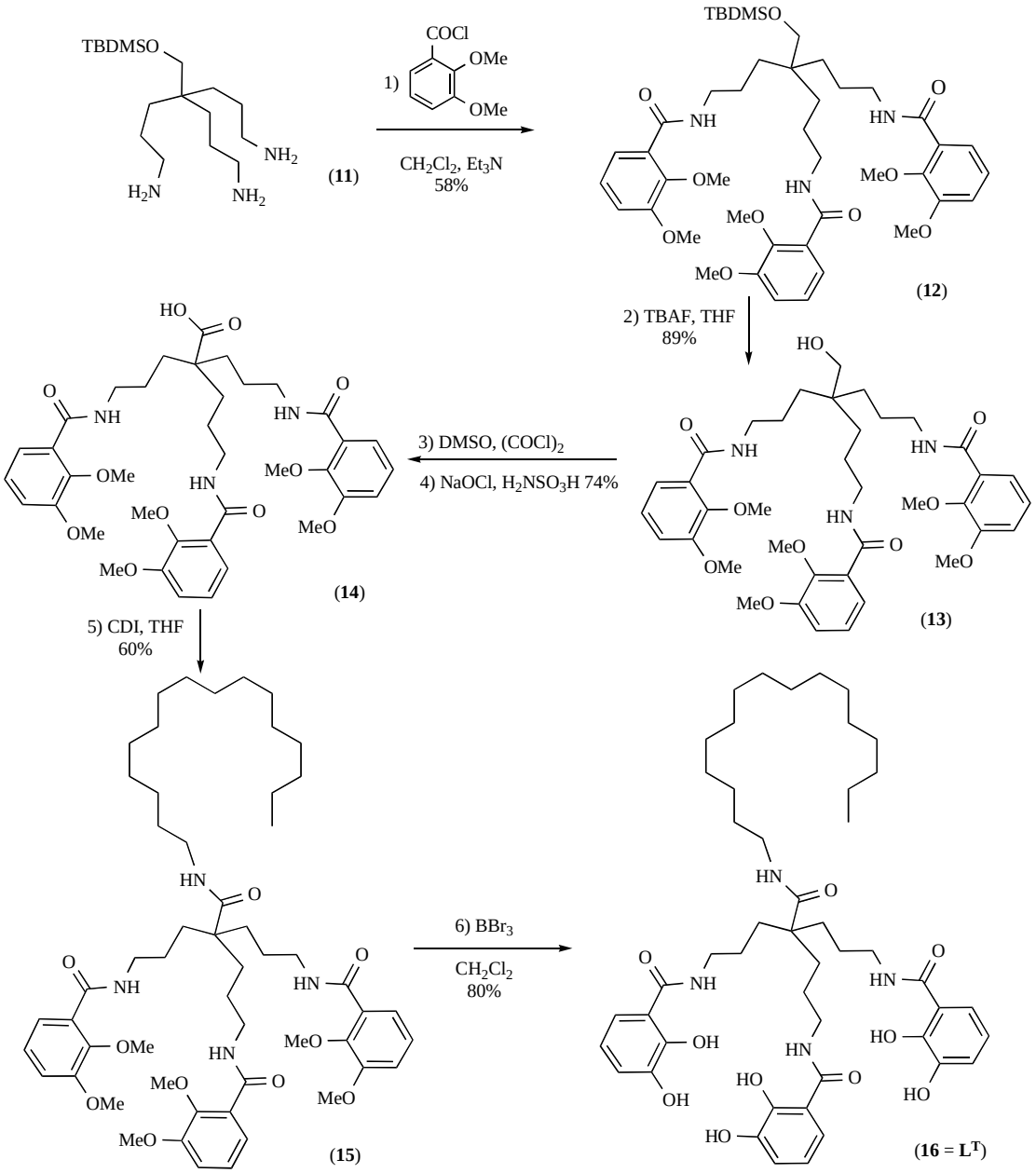
Then, the tripodal ligand (**16**) = ($\mathbf{L}^{T}$) was achieved as depicted in Scheme **3**. The key reactions are the oxidation steps 3) and 4) resulting in the formation of the carboxylic acid (**14**) suitable for further coupling after activation with CDI.

It was not a surprise to notice that the primary amine functions are not compatible with the aldehyde in (**19**): cyclisation readily occurred to produce the very stable bicyclic aminal (**20**) in 70% yield (Scheme **4a**), but it was quite unexpected to notice that the nitrogen atom of amides (**21**) were also still enough nucleophilic to react similarly with the –CHO group (see Fig. (**4b**)).

Recently we have improved the yield and the simplicity of the synthesis of the similar sulfonated ligand (**26** = $\mathbf{L}^{S10}$) by substituting the benzoyl chloride by its methyl ester counterpart which is more stable and less prone to hydrolysis (Scheme **5**) [24]. This strategy allows the use of 2,3-dihydroxybenzoic acid (**23**) and so avoids the final and often troublesome deprotection step of the catechol group

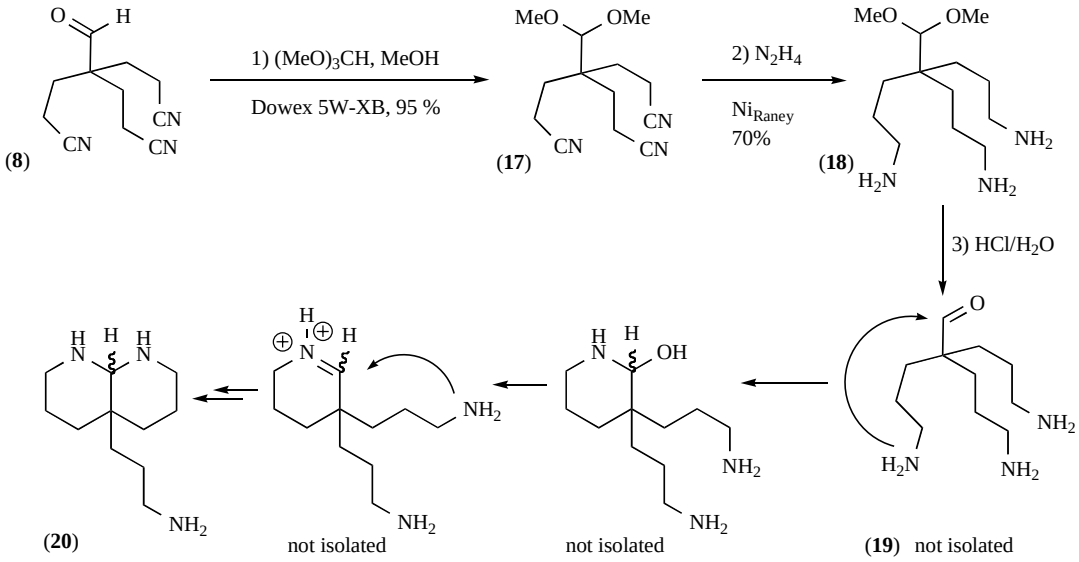


Scheme 2. Synthesis of the key tripodal scaffold (**11**).

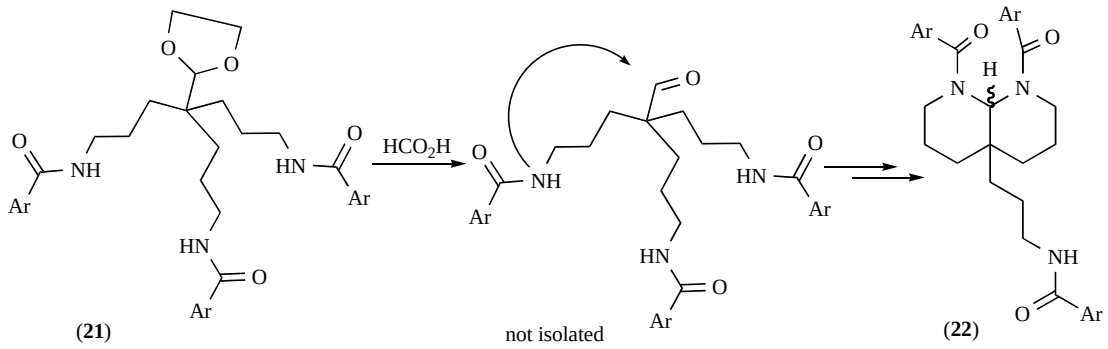


Scheme 3. Synthesis of the tripodal ligand (**16** = $\mathbf{L^T}$).

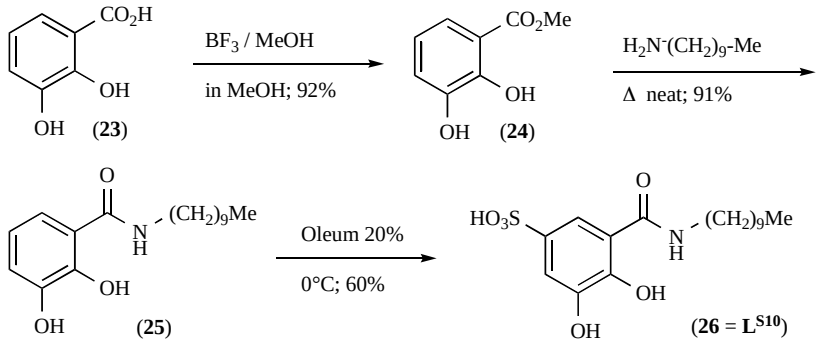
4a: Formation of bicyclic aminal (**20**)



4b: formation of bicyclic amidal (**22**)



Scheme 4. Cyclization of the scaffolds (**18**) and (**21**).



Scheme 5. Synthesis of the hydrophilic ligand (**26** = $\mathbf{L}^{S10}$) without protection of the catechol [24].

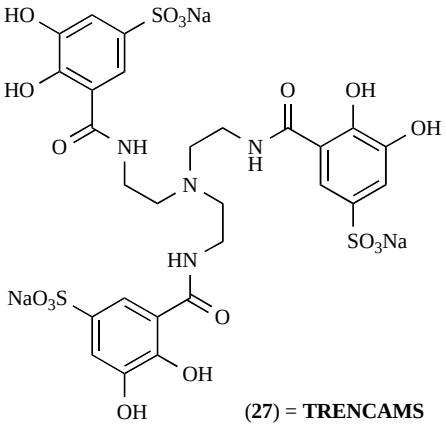
by BBr_3. But due to the lower reactivity of the ester, it is necessary to heat sufficiently in order to obtain significant reaction with the amine.

The sulfonation allows solubility in water and these ligands with a long alkyl chain and their iron(III) complexes have exhibited interesting tensioactive properties and formation of vesicles which mimic the Marinobacter's siderophores [24].

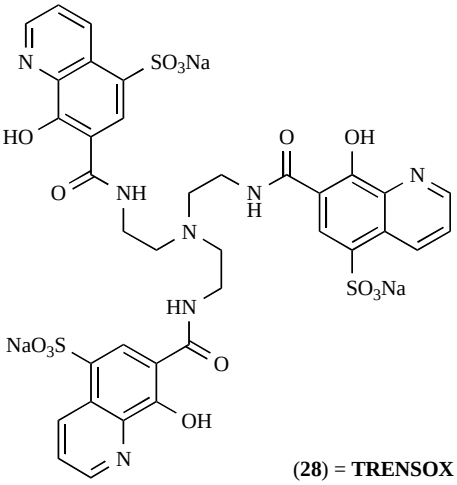
2. SYNTHESIS OF MIXED LIGANDS BASED ON CATECHOL AND QUINOLINE GROUPS

The synthesis of mixed tripodal ligands based on (i) two hydroxypiridinonate and one catechol moieties, and (ii) two hydroxypiridinonate and one 2-hydroxyisophtalamide groups has been published elsewhere [25]. In another hand, it has been shown that the *tris*catechol ligand (**27** = TRENCAMS, Fig. (**3**)) is a stronger ferric chelator than the *tris*hydroxyquinoline analogue (**28** = O-TRENSOX, Fig. (**3**)) at p[H] > 7 and that the opposite sequence is observed at p[H] < 7 [26,27].

In order to obtain an efficient chelator of iron(III) in a large range of p[H], we have synthesized mixed tripodal siderophores with both catechol and 8-hydroxyquinoline moieties [28] TRENSOXCAMS2 (**32**) = $\mathbf{L}^1$ and TRENSOX2CAMS (**36**) = $\mathbf{L}^2$ (Fig. (**4**)). These molecules belong to a family of tripodes with a *tris*(2-aminoethyl)amine group anchoring arms which bear bidentate

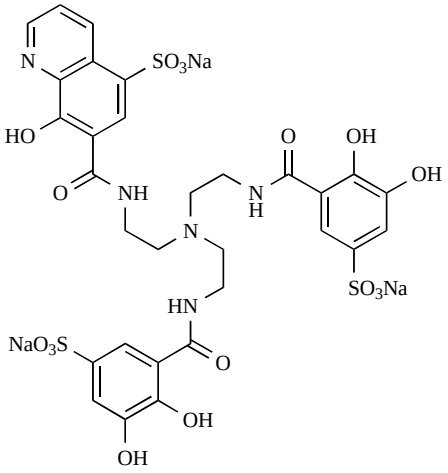


(**27**) = **TRENCAMS**

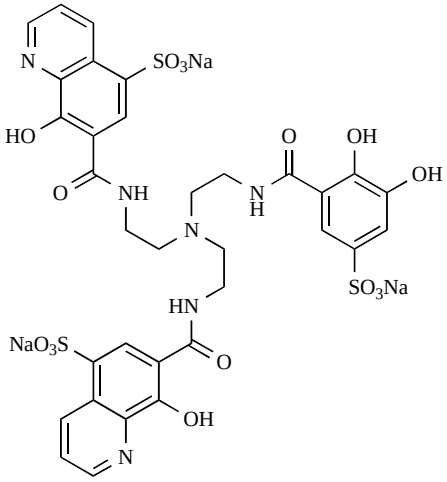


(**28**) = **TRENSOX**

Fig. (3). Chemical formulae of (**27**) = TRENCAMS and (**28**) = TRENSOX.



TRENSOXCAMS2 (**32**) = $\mathbf{L^1}$: pFe = 32.3



TRENSOX2CAMS (**36**) =$\mathbf{L^2}$: pFe = 31.6

Fig. (4). The mixed ligands TRENSOXCAMS2 ($\mathbf{L^1}$) and TRENSOX2CAMS ($\mathbf{L^2}$), pFe calculated at pH = 7.4, [L]/[Fe^{+3}] = 10.

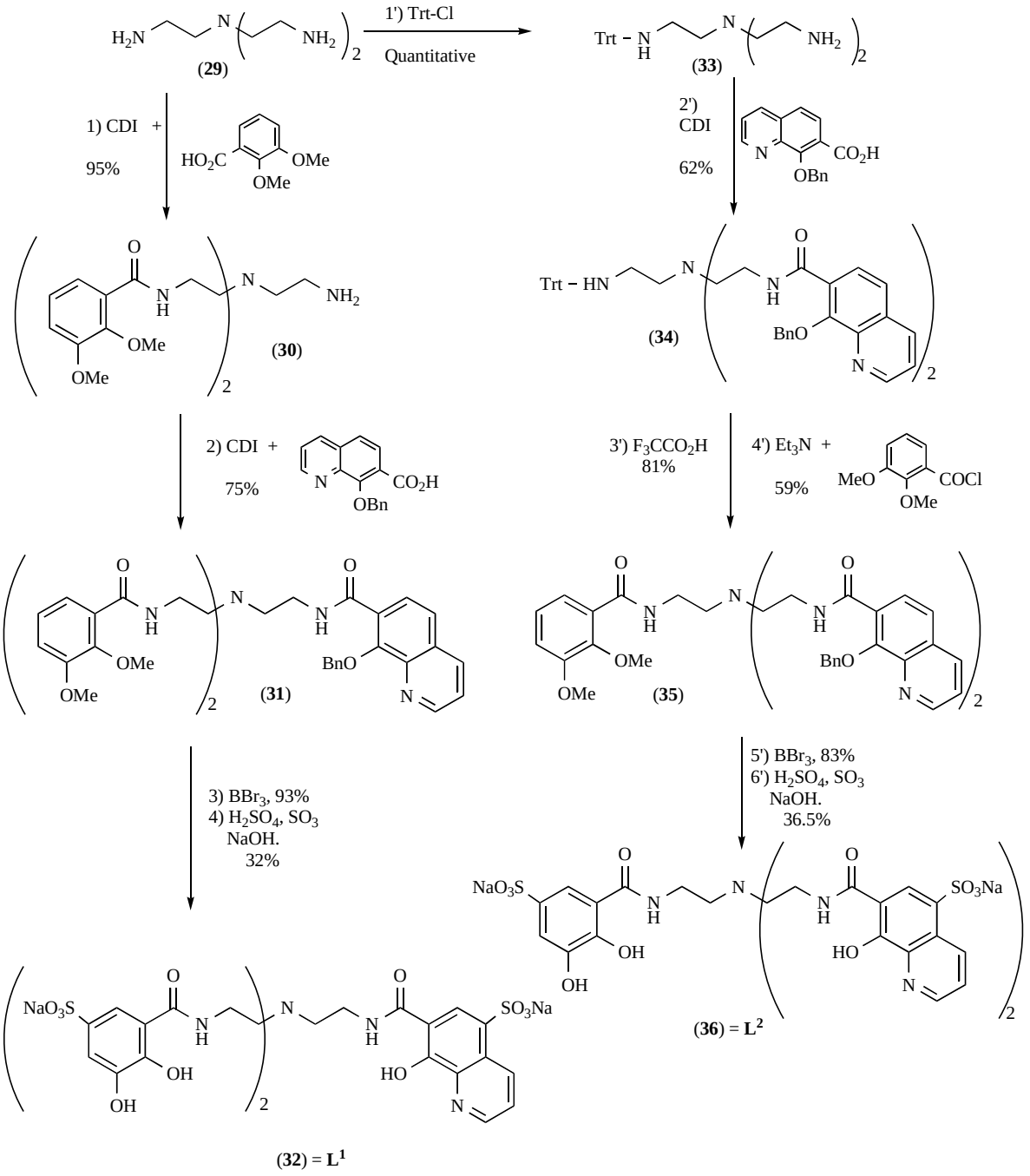
chelating subunits (namely either 5-sulfo-8-hydroxyquinoline-7-carbamoyl group or 5-sulfo-2,3-dihydroxybenzoyl unit).

The synthesis of the mixed hexadentate ligands is presented in Scheme **6**. A direct route was designed for the synthesis of ($\mathbf{L^1}$). The two catechol subunits of ligand ($\mathbf{L^1}$) were connected to the tripodal scaffold TREN (**28**) by direct condensation of two equivalents of 2,3-dimethoxybenzoic chloride with one equivalent of (**28**) (step 1, Scheme (**6**)), then the 8-hydroxyquinoline subunit was grafted onto the free primary amine group of by coupling with activated (CDI) 7-carboxy-8-hydroxyquinoline in a satisfactory yield of 75% (step 2, Scheme (**6**)). For the synthesis of ($\mathbf{L^2}$) the protection of one arm of TREN (**28**) with a trityl group is required because preliminary results showed that without the trityl group the di-8-hydroxyquinoline grafted TREN was very difficult to purify and produced low yield. The tritylation procedure involved was very easy to perform: when trityl chloride was added to an aqueous solution of TREN, the monoprotected TREN product (**33**) precipitated preventing a second tritylation. If the phenol groups were protected with benzyl groups for quinoline and methyl groups for the catechol, both deprotection of (**31**) and (**35**) were performed with BBr_3 in CH_2Cl_2 (steps 3 and 5', Scheme (**6**)). Finally, regiospecific sulfonation in position 5 of both 8-hydroxyquinoline and catechol subunits afforded the hydrosoluble ligands ($\mathbf{L^1}$) and ($\mathbf{L^2}$). The sulfonated ligands were obtained as their sulfonic acids instead of the more usual sodium salts; this allowed a more accurate purification (sodium sulfonate salts are often contaminated with Na_2SO_4).

3. SYNTHESIS OF A NATURAL SIDEROPHORE, QUINOLOBACTIN [29]

Recently, a true and unique 8-hydroxyquinoline siderophore has been identified from transposon mutant strain 3G6 of *Pseudomonas fluorescens* ATCC 17400 which was deficient in pyoverdine production [30]. This iron-chelating molecule was identified as 8-hydroxy-4-methoxy-quinaldic acid and designated quinolobactin (**41**). Since quinolobactin was first obtained in minute amount from a strain of *Pseudomonas fluorescens*, such a low quantity precludes the determination of properties like pKa or pFe. Neuenhaus *et al*. proposed a synthesis of this siderophore but no experimental detail was provided [31]. We have synthesized quinolobactin according to a straightforward synthesis described in Scheme **7**.

In this synthesis, the quinolobactin methyl ester (**40**) could be obtained in one-pot three steps starting from xanthurenic acid (**37**) which is also the starting product in the biosynthesis pathway. For the preparation of (**38**), thionyl chloride in excess proved to be more advantageous than $POCl_3$ the usual chlorurating agent used for such transformation. It is more conveniently distilled off than $POCl_3$ and gives better yield with better purity. When reacting (**38**)



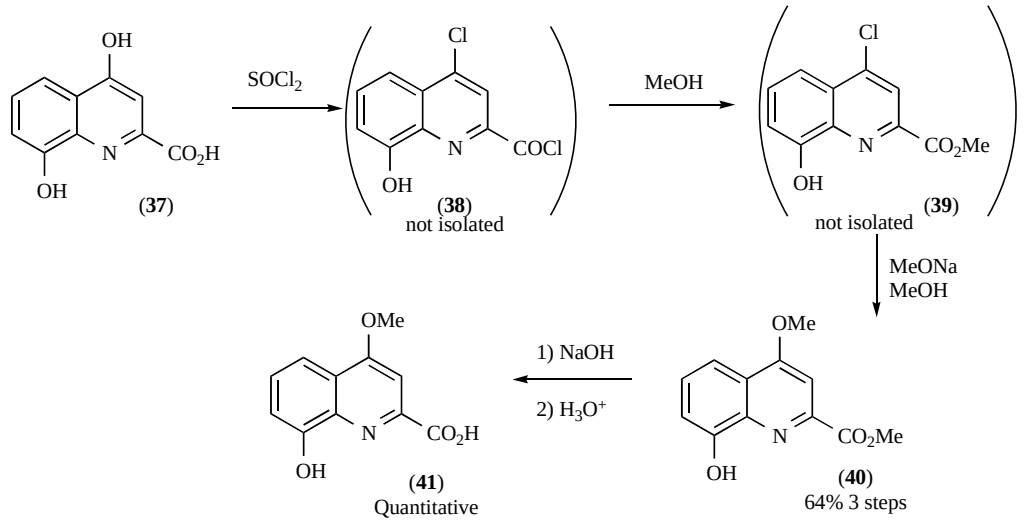
Scheme 6. Syntheses of TRENSOXCAMS2 (**32** = $\mathbf{L^1}$) and TRENSOX2CAMS (**36** = $\mathbf{L^2}$).

with dry methanol and then with sodium methylate, esterification (product (**39**), not isolated) and chloro displacement by SNar occurred very readily, producing the methyl ester of quinolobactin (**40**) in a satisfactory yield of 64% for 3 steps. Interestingly, if the carboxylic acid was not esterified, no SNar occurred since the first reaction observed was the formation of carboxylate anion with a delocalized charge on the aromatic nucleus which impeded further anionic attack like sodium methylate (Scheme **8**).

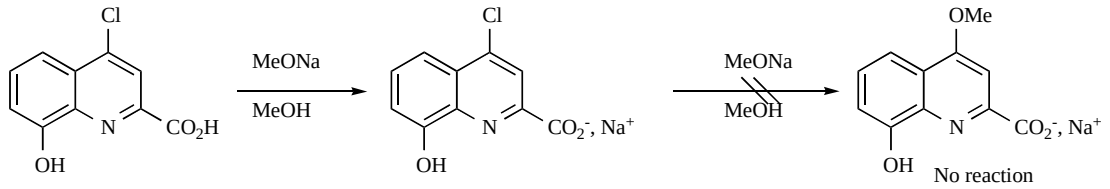
Quinolobactin (**41**) was finally obtained in excellent yield after saponification of the ester moiety and protonation. With gram amount of quinolobactin we were able to isolate the ferri-Quinolobactin $[Fe(Quinolobactin)_2]^-$ and the X-ray structure was established.

4. OXINOBACTIN, A BIOMIMETIC SYNTHETIC ANALOG OF ENTEROBACTIN INVOLVING 8-HYDROXYQUINOLINE CHELATING SUBUNITS

The recognition pattern of the ferri-siderophores is often sensitive to the chirality of the metal center which is also induced by the chirality of the ligand derived from naturally amino-acids [32]. This is the case with enterobactin (Fig. (**5a**)), the most efficient siderophore produced by *Escherichia coli* and *Salmonella typhimurium*. It derives from the naturally *L*-serine, forming a macrocyclic trilactone scaffold (**45**) (Fig. (**5b**)) tailoring an exceptional preorganization in terms of size of the cavity and orientation of the arms, favorable for the selective complexation of iron(III) ion. It has been shown that chelators based on 8-hydroxyquinoline complexing subunits could exhibit iron complexing abilities of the same order



Scheme 7. Quinolobactin synthesis according [29].



Scheme 8. Reactivity of sodium 4- chloro-8-hydroxyquinoline-2-carboxylate under SNar.

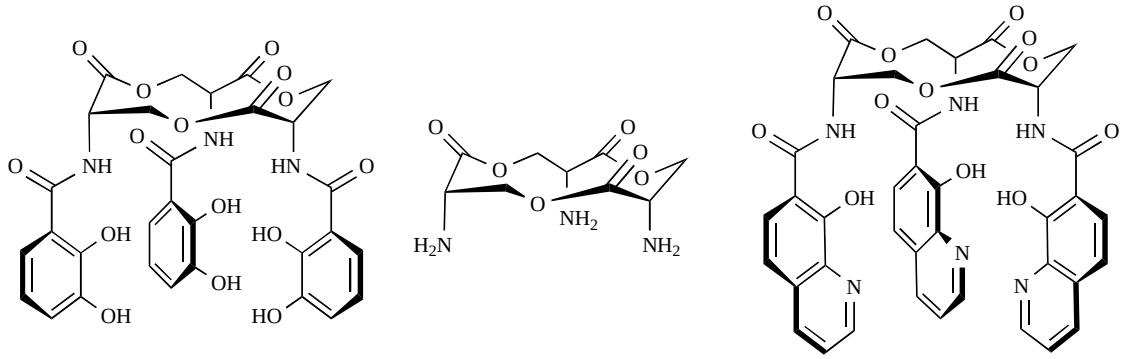


Fig. (5). a) enterobactin, **b)** trilactone scaffold (**45**) and **c)** the biomimetic oxinobactin (**52**).

as the catechol-based homolog's in neutral medium and proved largely higher complexing abilities in acidic medium [12]. So, it seemed interesting to design a chelator possessing the best natural siderophore molecular framework of enterobactin conferring the « chiral recognition area » but coupled to the 8-hydroxyquinoline chelating subunits (oxinobactin (**52**), Fig. (**5c**)) with the aim to obtain a chelating agent as strong as enterobactin (which could be recognized by the protein receptor) but with improved efficiency in acidic medium (a necessity if gastrointestinal absorption of the drug is planed).

Oxinobactin has been synthesized for this purpose [33]. The formation of the triserine lactone nucleus (**45**) (Fig. (**5b**)) constitutes the key intermediate. Previous methods were laborious and gave low yields. Corey [34] and Rastetter [35] obtained the macrocyclic lactone in 1% yield. Shanzer improved the preparation using a tin template, but the overall yield was still low (6%) in relation to the low-yield formation (26%) of a serine beta-lactone precursor (Fig. (**6a**)) [36]. Following this tin template approach, Gutierrez *et al*. presented a very efficient and experimentally facile synthesis of the trilactone scaffold (85%) starting from methyl *N*-trityl-*L*-serinate using 2,3-dibutyl-1,3,2-dioxastannolane (Fig. (**6b**)) as a template for the cyclo-oligomerization [37].

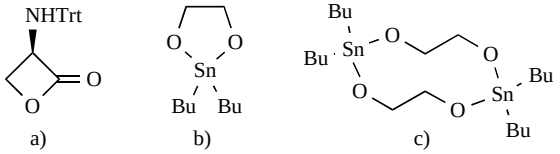
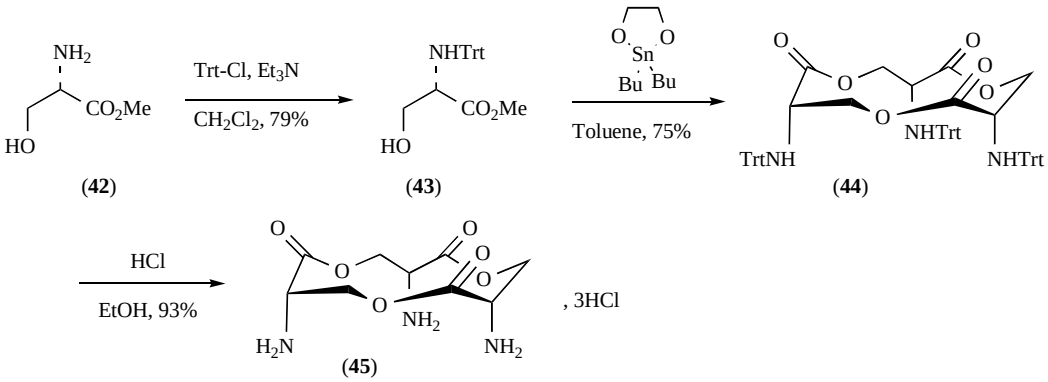
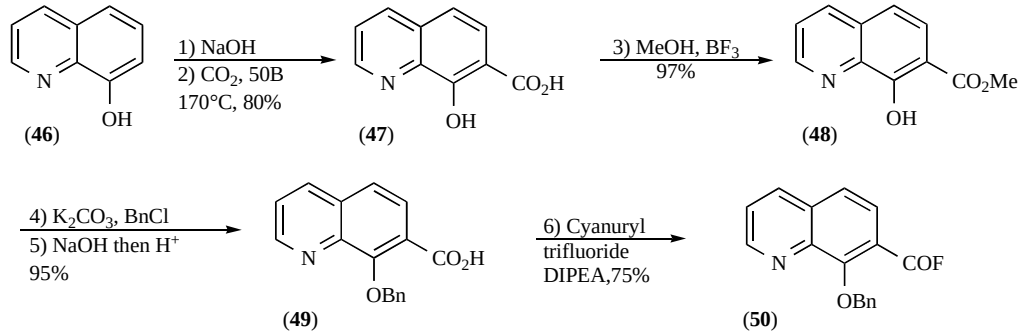


Fig. (6). a) *N*-trityl serine beta-lactone, **b)** 2,3-dibutyl-1,3,2-dioxastannolane and **c)** 1,1,6,6-tetra-n-butyl-1,6-distanna-2,5,7,10-tetraoxacyclodecane.

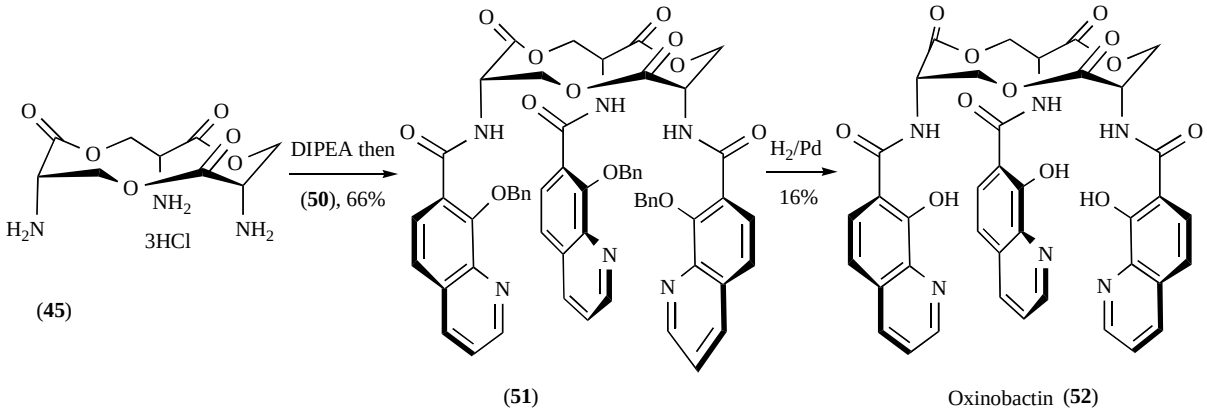
The 1,1,6,6-tetra-n-butyl-1,6-distanna-2,5,7,10-tetraoxacyclodecane (Fig. (**6c**)) used as a tin template seems to be less efficient since only 56% yield of trilactone was obtained by Raymond and col [38]. Indeed, in our hand the organotin-mediated trimerization of methyl-*N*-trityl-serinate (**43**) proved to be more efficient with the



Scheme 9. Preparation of the trilactone scaffold (**45**) starting from methyl *L*-serinate.



Scheme 10. Bidentate 8-hydroxyquinoline synthesis and activation of the carboxylic group.



Scheme 11. Oxinobactin (**52**) from scaffold (**45**).

dibutylstannolane (Scheme **9**). The cyclo-oligomerization could be equally realized in refluxing xylene or toluene in the same concentrations resulting in similar yield but with longer reaction times (24h and 48h respectively).

Removal of the *N*-trityl protecting group of (**44**) under acidic conditions in ethanol gave the trilactone framework as triamine trihydrochloride (**45**) in excellent yield. It should be noticed that no transesterification reaction could be observed during this step, underlying the exceptional acidic stability of the scaffold. The bidentate subunits were prepared starting from the commercially available 8-hydroxyquinoline (**46**) (Scheme **10**).

Carboxylation of (**46**) under Kolbe-Schmitd conditions and protection of the phenol group as a benzylic ether afforded the acid (**49**) which was then activated *via* the acid fluoride (**50**). The acid fluoride was chosen in place of the more usual acid chloride because it is more stable toward hydrolysis, it could be purified by CPL and characterized by ^{19}F NMR spectroscopy and hence it is more selective for the amide step formation. For this transformation, di-*iso*-propyl-ethylamine (DIPEA) was necessary as a proton scavenger, Oxinobactin (**52**) was then obtained by reductive hydrogenation of (**51**) in which the competitive hydrogenation of the pyridine nucleus explains the low yield obtained (Scheme **11**).

Removal of the benzylic protective group could be achieved without reduction of the pyridine nucleus using poisoned catalyst $Pd/BaSO_4$ or in the presence of quinoline.

This is the first example of synthetic analog of enterobactin that retain the trilactone ring with 8-hydroxyquinoline binding subunits, constituting a lipophilic ligand for iron chelation or for other metal cations as Ga^{3+}.

CONCLUSION

In this minireview, we have selected few examples of iron chelator syntheses. We have chosen these examples in different field of interest: (i) amphiphilic chelators, (ii) mixed ligands, (iii) a natural siderophore, (iv) an artificial siderophore possessing the

properties of recognition of a natural homolog. While not exhaustive, these examples underline the various areas in which synthetic iron chelators are of interest and illustrate the great variety of chemistry encountered in the field of bioorganic and bioinorganic chemistry. It can be concluded by enouncing « the five commandments » to the organician chemist for the syntheses or iron chelators:

- The design of ligands needs a rational approach for the understanding of iron(III) complexing abilities.

- The octahedral arrangement of donor atoms is the most favorable geometry. Hexadentate ligands (usually *tris* bidentate) allow a preorganization of the coordination sphere, well-suited for high pFe.

- Natural siderophores and most of their synthetic models contain three catecholate or hydroxamate groups. Nevertheless, efficient chelators have been developed, involving other chelating subunits such as 8-hydroxyquinoline.

- The water solubility and the hydrophilic/lipophilic balance are an important characteristics related to the assimilation of the chelator by living systems.

- Some additional properties may be needed for a precise function: probes, diagnostic tools, and vectorisation.

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