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Original article

# A new class of bioactivable self-immolative *N*,*O*-ligands

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ABSTRACT

A hexadentate ligand built on an amine-bis(phenol) skeleton with an aminal, self-immolative moiety is presented. Synthesis of the ligand is convenient and relatively high yielded. Moreover, it enables synthesis of many derivatives, both in the amino-phenol and aminal fragment (various heterocycles). Once the final hexadentate ligand is synthesized via the Katritzky reaction, it becomes prone to hydrolysis. Bioactivation by β-galactosidase cleaves the glycosylic bond and a spontaneous collapse of the aminal fragment occurs, thus leading to a pentadentate chelate. This bioactivation has been shown for pyrazole, 1,2,4-triazole and benzotriazole derivatives.



## 1. Introduction

Classic amino-phenolate ligands, with the aminobis(phenolate) root, have a well-established chemistry [1,2] for a broad range of metals [3–5]. They are used because of their convenience in synthesis, with huge possible derivatives expressing high affinity to metal chelation, which results in good product constants. Amino-phenolates are a key fragment of the protein inhibitor [6–8] and mimic the catechol oxygenase active site [9,10]. Conversely, great interest has been focused on bioactivable species, which have potential application in a system where a measurable physical or chemical stimulus appears [11–16]. The introduction of a pendant, bioactivable arm is one approach that has recently been applied for smart contrast agents [17–22]. Bioactivation by enzymatic cleavage of a non-directly coordinating fragment is followed by the self-immolative release of a coordination site. This results in an observable change in the relaxivity, so that enzyme activity can be monitored non-invasively [23–25]. Here we present a new class of bioactivable, self-immolative amine-phenol hexadentate ligand dedicated to d-block metals. The idea was to design a delicate system which, because of its nature, would be difficult to separate out from the reaction mixture. Yet it could be complexed and, when exhibiting higher stability, purified and applied to the target system. Once activated by an enzyme, the system can be monitored by appropriate instrumentation – Scheme 1.

In this paper we present ligand synthesis and the results of bioactivation experiments.

## 2. Results and discussion

### 2.1. Synthesis of the pentadentate ligand **3**

Synthesis of the target ligands **7a**–**7f** was multistep (Scheme 2.). However, the main purpose was the high selectivity of each step since separation of the potential products (i.e. mono- and di-*N*-alkylation) could be very problematic. Initially, we attempted to build the 2-hydroxybenzyl fragment by a reaction of salicylamide reduction with $LiAlH_4$, as reported by Parker [26]. Unfortunately, the yield was very low and the desired product was difficult to separate from the reaction mixture. Therefore, we abandoned this route. Siegl et al. described the synthesis of compound **1** in a Mannich-type reaction from phenol, HCHO and 2-aminoethanol [27]; however, our attempt to synthesize compound **1** by this method failed. Thus, the amine skeleton **1**–**3** was synthesized as follows: *N*,*N*-bis(2-hydroxyphenylmethyl)-2-aminoethanol (**1**) was obtained in a two-step *one-pot* reaction of the reductive amination of 2-aminoethanol with salicylaldehyde. The reaction conditions were similar to those described by Hinshaw [28]. $NaBH_3(CN)$ was applied as a reductive agent because of its higher

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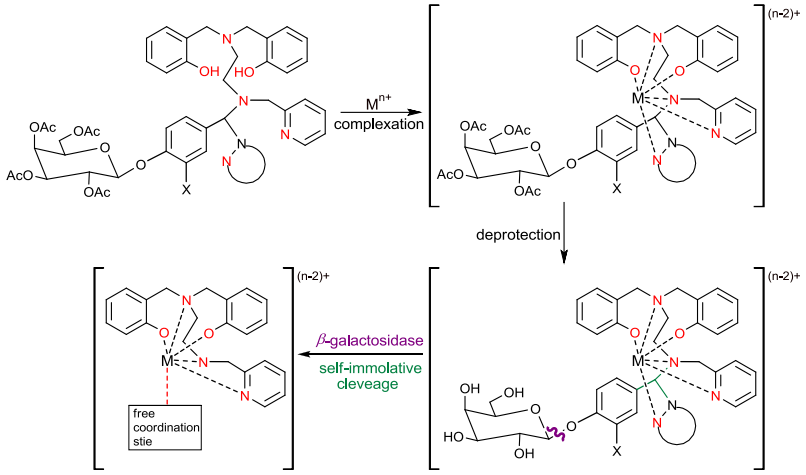
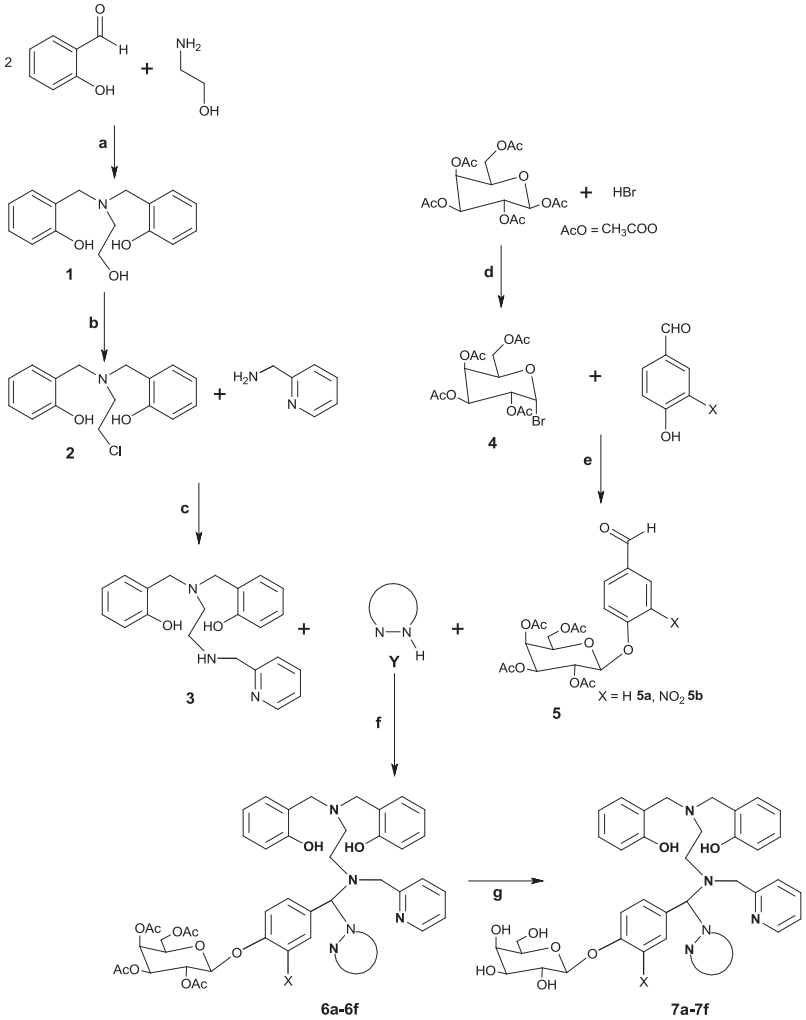



**Scheme 1.** Bioactivable, self-immolative ligand synthesis, complexation and activation – a concept.

stability than regular $NaBH_4$, especially in an acidic environment [29,30]. Since the synthesis is a multistep condensation followed by reduction, relatively low yields of 24–34%, depending on the scale, are quite satisfactory. No monobenzyl derivative was identified in the post-reaction mixture. The purified product, **1**, was subjected to $SOCl_2$ treatment, thus leading to chlorinated product **2**. It was crucial to use freshly distilled thionyl chloride; otherwise, the reaction would fail. During the reaction a waxy,




**Scheme 2.** Synthesis of ligands. Coordination sites are bolded. *Reagents and conditions*: (a) MeOH, 1.5 h, HCl/MeOH, $NaBH_3(CN)$, 72 h, then the next batch of salicylaldehyde, $NaBH_3(CN)$ 72 h, **1** 34%; (b) $CH_2Cl_2$, $SOCl_2$. 24 h, rt 10%, $Na_2CO_3$ **2** 90%; (c) EtOH, reflux 2 h, **3** 77%; (d) $Ac_2O$, HBr/AcOH, **4** 94%; (e) MeCN, $Ag_2O$, 4–4.5 h rt, **5a** 89%, **5b** 73%; (f) benzene, reflux in Dean–Stark app. 8–70 h – Table 4; (g) MeONa/MeOH, overnight, rt, $CO_2$.