DOI: 10.1002/ejic.200800419

Effective Repression of the Fragmentation of a Hexadentate Ligand Bearing an Auto-Immolable Pendant Arm by Iron Coordination

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Keywords: Iron / Macrocyclic ligands / Prodrugs / Auto-immolable spacer / Low-spin complex

A diamagnetic ferrous complex (**1**) (MRI silent) is presented that consists of a macrocyclic hexadentate ligand (**7**) bearing an auto-immolable arm, as seen in organic prodrug design. This arm constitutes a phenylogous N/O acetal "locked" by glycosylation. Enzymatic glycolysis is hypothesized to lead to a phenol intermediate (a phenylogous hemiaminal) that fragments spontaneously thereby liberating a paramagnetic ferrous complex (MRI active). This paper describes the synthesis of ligand **7** and complex **1**, and their respective reaction with β-galactosidase, the target enzyme. While ligand **7** alone fragments swiftly to the pentadentate ligand dptacn (monitored by LCMS analysis) upon in vitro enzymatic conversion, the phenol resulting from glycosyl removal from complex **1** accumulates in the buffered reaction mixture without any apparent fragmentation. Two independent explanations are put forward: metal coordination leads to rigidification of the ligand skeleton with concomitant kinetic inhibition of fragmentation or to the liberation of enough extra free energy to shift the thermodynamic equilibrium towards the starting material.

Introduction

Molecular imaging is an immense and rapidly expanding field dedicated to the elucidation of the molecular basis of life and disease.[1] The mostly invasive, and often lethal, nature of classical approaches, such as fixation (histology) of the living species, renders the resulting observations somewhat unreliable. It is therefore desirable to develop methods for in vivo imaging with minimal interference with the species under scrutiny. This would also allow for the very useful temporal resolution of the results.

We set out to develop a molecular probe for a specific enzymatic activity for magnetic resonance imaging (MRI).[2] A number of smart contrast agents have already been introduced, among them those that detect copper, zinc, or calcium ions[3–6], as well as those that reveal a specific enzymatic activity.[7–12] They all have in common the presence of a gadolinium(III) atom at their center that is a permanently paramagnetic lanthanide ion. We have opted for iron(II) as this paramagnetic center in order to capitalize on its exceptional property of adopting a diamagnetic as well as a paramagnetic state depending on ligand-field strength.[13,14] A pair of binary, mononuclear iron(II) complexes in a low-spin and a high-spin state, respectively ([Fe-*t*ptacn]^{II} and [Fe-*d*ptacn]^{II}), have thus been identified as a promising point of departure for the design of enzyme-responsive MRI contrast agents that operate in an off/on mode.[2]

Monitoring enzymatic activity by MRI is a very attractive perspective for a number of biomedical reasons.[15–19] However, for two reasons it would also be appealing from a technological viewpoint: (a) MRI suffers from low sensitivity,[20,21] but the development of MRI-active probes that are susceptible to a particular enzymatic activity will lead to a more or less pronounced *amplification* effect according to the in vivo turnover rate by the enzyme of such an artificial substrate, an effect that is exploited in diverse biotechnology applications such as ELISA, as well as in (organic) prodrug design. The presence of one protein molecule thus equals a vast number of activated imaging probes. (b) Among the competing imaging techniques only optical methods allow the design of enzyme-responsive agents; ultrasound imaging, X-ray-based CT and PET (that detects γ-ray emitting radioactive tracers) do not appear to lend themselves to the development of tracers that show a signal change induced by chemical (enzymatic) modification.

Results and Discussion

In this paper we present the first MRI-silent (off) molecule candidate (**1**) based on [Fe-*t*ptacn]^{II} that is hypothesized to fragment upon enzymatic conversion. Figure 1 depicts **1** that may, by judicious molecular design, be rendered susceptible to a number of mostly (but not exclusively) hydrolytic enzymatic activities. Compound **1** should be effec-

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Supporting information for this article is available on the WWW under http://www.eurjic.org or from the author.

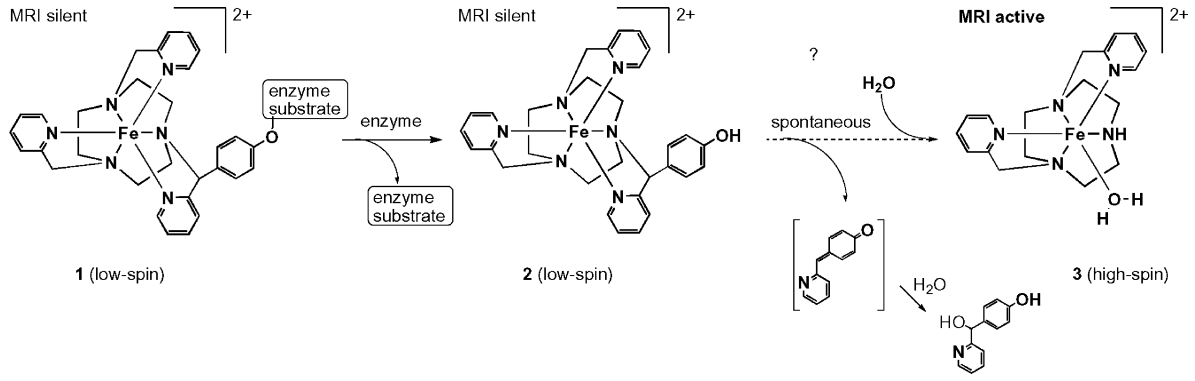

Figure 1. Hypothesized enzymatic conversion and subsequent fragmentation from a low-spin to a high-spin ferrous complex.

tively converted by the targeted enzyme into intermediate **2**, which, in return, is supposed to fragment spontaneously into an MRI-active species (**3**) via elimination of a fragment containing one nitrogen coordination site. Consequently, one coordination site on the iron center should be vacated, occupied by a water molecule, and **3** thus becomes an effective relaxation-modifying agent for neighboring water protons (see ref.[2] for values of the effective magnetic moment μ_{eff}, the longitudinal relaxation time $T1$, and relaxivities r_1 of **3** and a derivative of **1**, respectively).

The hypothesis that **2** spontaneously fragments (Figure 1) is based on the fact that **2** contains a moiety (Figure 2, gray) that is reminiscent of a hemiaminal. Under reasonably dilute conditions, the equilibrium of hemiaminal formation is well known to be largely positioned on the bimolecular side; in addition, establishment of this equilibrium is fast.[22,23] The moiety as utilized in **2** is in fact a phenylogous hemiaminal, thus promising similar electronic features but also allowing the enzymatic reaction with **1** to proceed rather effectively as a consequence of the good phenolic leaving group. However, an important difference with a simple phenylogous hemiaminal is the fact that in **2** the nitrogen fragment and the carbon fragment are actually linked to one another via a three-membered (-C–N–Fe-) buckle including the coordinative bond to the metal center. It thus remains to be seen if spontaneous fragmentation takes place in physiological media. The pendant arm in **1** may also be compared with auto-immolable spacers generating high-energy quinone–methide intermediates as found in the field of (organic) prodrug development. Yet such spacers usually employ well-established leaving groups as for example carboxylates or carbamates.[8,12,24]

In this initial work, the hydrolase activity that is targeted is that of β-galactosidase (**1**, Figure 3). This enzyme is the product of a prominent *reporter gene* system.[25,26] Synthesis of β-galactoside **1** was achieved by first preparing the halide

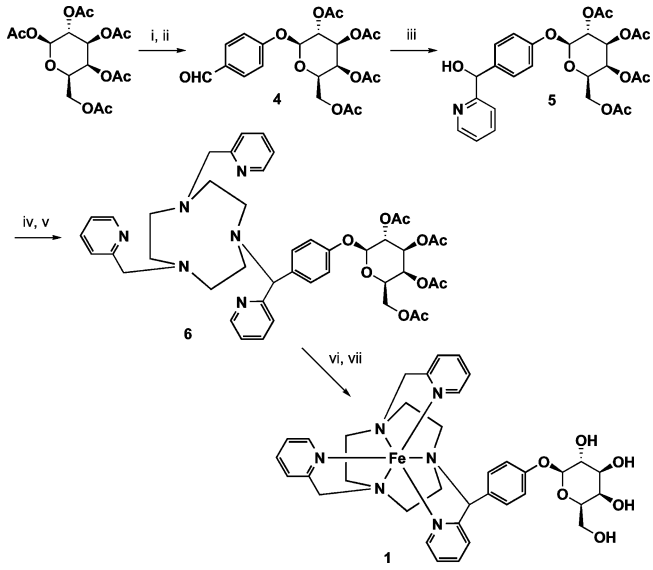

Figure 3. Synthesis of **1**. Reagents and conditions: (i) HBr 30% in AcOH, (ii) Ag_2O, *p*-hydroxybenzaldehyde, (iii) 2-PyrMgBr, (iv) $SOCl_2$, (v) dptacn (**9**), K_2CO_3, AcCN, 80 °C, 84%, (vi) MeONa, MeOH, (vii) $[Fe(H_2O)_6][BF_4]_2$, degassed MeOH.

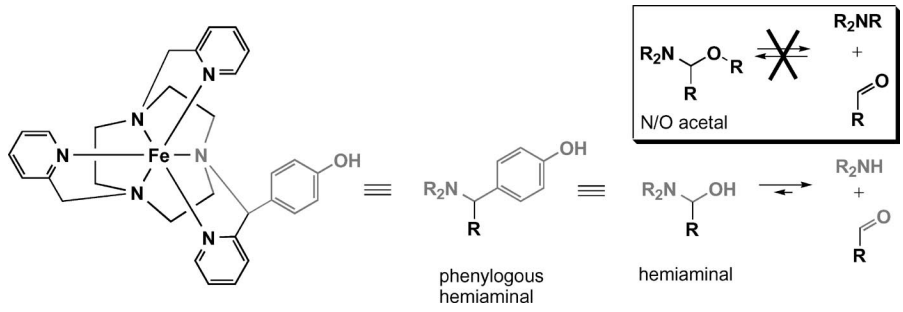

Figure 2. Pendant arm consisting of a phenylogous hemiaminal and its homology to parent acetal chemistry.

of alcohol **5** in four steps from commercial β-galactose pentaacetate. Bromination of the latter[27] and subsequent coupling to *p*-hydroxybenzaldehyde by the Königs–Knorr method[28] furnishes an aldehydic synthetic intermediate (**4**) that is treated with pyridine magnesium bromide[29] to obtain a secondary alcohol **5**. Chlorination of the latter with sulfonyl chloride preceded the coupling to the pentanitrogen macrocyclic ligand dptacn.[30] The glycoside unit in the resulting hexadentate ligand **6** was deprotected by standard methods using sodium methylate in methanol. The synthesis of **1** was complete by reacting **6** with $[Fe(H_2O)_6][BF_4]_2$ under anaerobic conditions.

In order to be able to monitor the reaction of candidate molecule **1** with target enzyme β-galactosidase under physiological conditions, a powerful analysis method had to be found that would ensure reliable identification of the starting compound, any intermediates, and the desired final complex. Metal complexes of the likes of **1** and **3** are generally identified and characterized by elemental analysis, magnetic moment measurements, UV/Vis spectroscopy (less often by IR) in organic solvents, X-ray analysis, and rather rarely by NMR and Mössbauer spectroscopy. From the outset, any detection method applied to the chemical transformation of **1** in this project had to be compatible with the more or less complex physiological nature of the sample. Such a technique was recognized in the form of high performance liquid chromatography coupled simultaneously to UV analysis and mass spectrometry (LCMS).

Candidate complex **1** (as well as its homologue [Fe-*t*ptacn]^{II}[2]), intermediate **2**, and target complex **3** were found to be stable during HPLC analysis and to be ionizable by electrospray ionization (ESI) and thus identifiable by mass detection. Enzymatic conversion of **1** proceeded efficiently as expected; one of its diastereomers (see the twin peaks at 3.7 min in Figure 4a) showed a slightly higher conversion rate than the other. The intermediate phenol **2** thus produced accumulated in the sample without any apparent willingness to fragment; no trace of the desired complex **3** was detected (Figure 4a).

When the same experiment was carried out with compound **7** (being the underlying ligand of complex **1**), fragmentation of intermediate **8** (Figure 5) to dptacn (**9**) was so fast that any accumulation of **8** was not observed (Figure 4b). This illustrates the rarely explored stabilization effect of any metastable molecular species (such as a phenylogous hemiaminal) if the two possible fragments are held together by common coordination to the same metal center. Here, severe rigidification may prevent the system from adopting conformations leading to transition states with reasonable energy barriers (kinetic inhibition). Alternatively, additional free energy release upon coordination of the two fragments to the metal center may be the cause, thus shifting the thermodynamic fragmentation equilibrium to the left.

In spite of the lack of fragmentation of phenol **2**, the here applied intelligent spacer technology using a phenylogous hemiaminal has been proved to contribute three advantages: (a) The phenolic character of the glycoside leads to rapid enzymatic conversion. (b) The site of enzymatic recognition is remote to the metal complex, likewise maximizing enzyme kinetics. (c) The experimenter has control over the choice of the molecular moiety coordinating the metal and hence also over the electronic spin state and the absence of any influence on the proton relaxation time by the resulting complex.

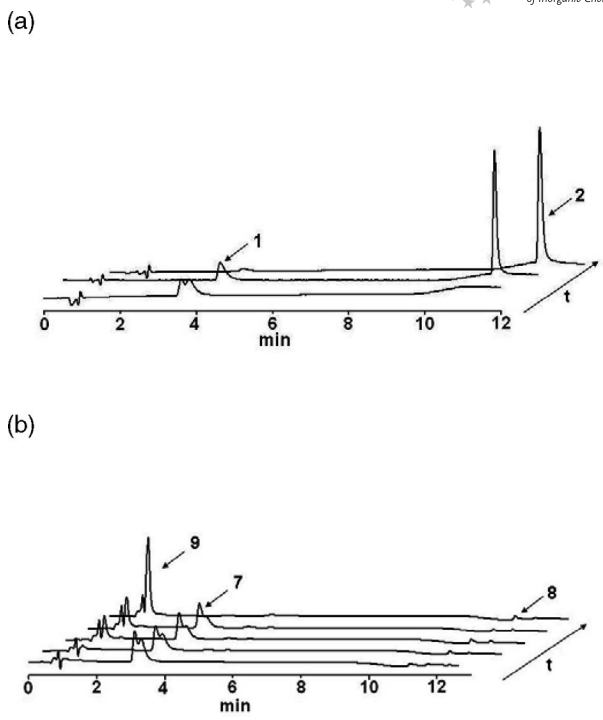

Figure 4. Time-dependent conversion by β-galactosidase of (a) **1** and (b) **7**, monitored by HPLC coupled with UV and mass analysis (ESI). Enzyme assay conditions: see Supporting Information. Chromatographic conditions: Zorbax Eclipse XDB-C8 5 mm 4.6 × 150. Mobile phase = 0.1 % formic acid in H_2O/AcCN (88:12) isocratic, 0.5 mL/min, 25 °C. UV detection at 399 (a) and 270 nm (b), respectively.

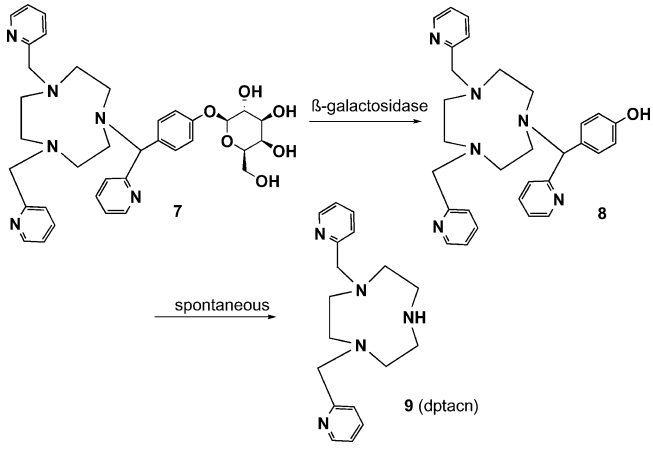

Figure 5. Spontaneous fragmentation of intermediate **8** into desired pentadentate ligand **9** after its generation by enzyme-catalyzed glycolosis of **7**.

Conclusions

Prodrug activation strategies for metal complexes are still very rare and require considerable additional research efforts on top of what has been invested in the development of organic prodrugs. The results in this paper have illustrated the considerable stabilization effect contributed to auto-immolable spacer units by metal complexation. This influence should be countered by rendering the ligand thermodynamically more labile before its complexation with the metal. Also, the issue of substitution kinetics[31] of the coordinating imine moiety (pyridyl or other) by water needs to be addressed.[32,33] To this end, studies of remote derivatives of **1** are currently in progress.

Experimental Section

All reactions were conducted under an inert atmosphere using Schlenk tubes and vacuum-line techniques. Solvents were degassed using standard procedures.

4-(Tetraacetyl-β-D-galactopyranosyloxy)benzaldehyde (4): Tetraacetyl-α-bromogalactopyranose (4.11 g, 10.0 mmol) in distilled AcCN (100 mL) was treated with Ag_2O (10.0 g, 42.0 mmol) and *p*-hydroxybenzaldehyde (1.22 g, 10.0 mmol). The mixture was stirred for 4 h before the solvent was evaporated. The resulting residue was taken up in ethyl acetate and filtered through a pad of silica gel to remove the metallic components. After evaporation, yellow oil was obtained that was purified by column chromatography (Et_2O). Compound **4** was obtained in crystalline form by slow evaporation of the solvent (3.04 g, 67%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 7.85 (d, J = 8.7 Hz, 2 H), 7.11 (d, J = 8.7 Hz, 2 H), 5.47 (m, 2 H), 5.17 (m, 2 H), 4.17 (m, 3 H), 2.19 (s, 3 H), 2.06 (s, 6 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.6, 170.2, 170.1, 170.0, 169.2, 161.2, 131.7, 116.7, 98.5, 71.3, 70.6, 68.4, 66.7, 61.3, 20.6, 20.5 ppm. M.p. 116.4 °C. HRMS: calcd. for $C_{21}H_{24}NaO_{11}$ [M + Na] 475.12163; found 475.12166.

[4-(Tetraacetyl-β-D-galactopyranosyloxy)phenyl](pyridin-2-yl)-methanol (5): 2-Bromopyridine (948 mg, 574 μL, 6.0 mmol) in THF (8 mL) was treated dropwise with isopropylmagnesium bromide (3.0 mL, 6.0 mmol, 2 M in THF) under argon at 50 °C for 2 h. The resulting solution was added at a rate of 0.5 mL/2 h to **4** (2.26, 5.0 mmol) in THF (18 mL) at room temperature, and the reaction mixture was stirred until complete consumption of **4**. The reaction was quenched with sat. NH_4Cl, extracted with CH_2Cl_2, and the combined organic phases dried with Na_2SO_4. Purification of the resulting residue by silica gel column chromatography yielded a colorless solid that was recrystallized in pure diethyl ether (yield 1.94 g, 73%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.57 (d, J = 4.7 Hz, 1 H), 7.63 (td, J = 7.6, 1.4 Hz, 1 H), 7.30 (d, J = 8.6 Hz, 2 H), 7.21 (t, J = 4.7 Hz, 1 H), 7.13 (d, J = 7.6 Hz, 1 H), 6.97 (d, J = 8.6 Hz, 2 H), 5.72 (d, J = 4.2 Hz, 1 H), 5.43–5.47 (m, 2 H), 5.19 (d, J = 4.2 Hz, 1 H), 5.08 (dd, J = 7.9, 4.2 Hz, 1 H), 5.01 (d, J = 7.9 Hz, 1 H), 3.97–4.22 (m, 3 H), 2.17 (s, 3 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 2.00 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.6, 169.5, 169.4, 168.66, 160.1, 155.9, 147.2, 137.6, 136.2, 127.7, 121.8, 120.6, 116.4, 99.0, 73.7, 70.3, 70.1, 68.0, 66.2, 60.7, 20.0 ppm. M.p. 138.2 °C. HRMS: calcd. for $C_{26}H_{29}NO_{11}$ [M + H] 532.18189; found 532.18186.

1,4-Dipicolyl-7-[4-(tetraacetyl-β-D-galactopyranosyloxy)phenyl]-(pyridin-2-yl)methyl-1,4,7-triazacyclononane (6): Compound **5** (600 mg, 1.1 mmol) in CH_2Cl_2 (15 mL) was treated dropwise with thionyl chloride (143 mg, 88 μL, 1.2 mmol) and stirred for 1 h. All volatile components were then thoroughly evaporated, and the resulting chloride was introduced into the next step as is. A solution of 2-[chloro(4-tetraacetyl-β-D-galactopyranosyloxy)phenyl]methylpyridine (356 mg, 0.6 mmol) and dptacn (**9**; 168 mg, 0.5 mmol) in AcCN (10 mL) was treated with K_2CO_3 (1.5 g, 11 mmol). The resulting suspension was stirred under argon at 50 °C overnight. The mixture was filtered at room temp., and the solid was washed with AcCN. The combined organic phases were evaporated, and the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH, 10:1 to CH_2Cl_2/MeOH/NH_4OH, 4:1:0.1). Hexaamine **6** was thus obtained as a yellow oil (327 mg, 74%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.48 (t, J = 4.4 Hz, 3 H), 7.63 (td, J = 7.6, 1.6 Hz, 3 H), 7.36 (d, J = 8.6 Hz, 2 H), 7.13 (m, 3 H), 6.89 (d, J = 8.6 Hz, 2 H), 5.42 (m, 2 H), 5.06 (dd, J = 7.9, 4.2 Hz, 1 H), 4.98 (d, J = 7.9 Hz, 1 H), 4.78 (s, 1 H), 3.97–4.22 (m, 3 H), 3.79 (s, 4 H), 2.96 (s, 4 H), 2.84 (d, J = 8.6 Hz, 4 H), 2.16 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 2.00 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.3, 179.2, 170.1, 169.3, 163.0, 160.4, 155.8, 148.9, 137.2, 136.4, 136.2, 129.8, 123.2, 122.6, 121.8, 116.7, 99.5, 70.8, 68.6, 66.8, 64.6, 61.3, 55.8, 55.5, 54.0, 20.6 ppm.

1,4-Dipicolyl-7-[4-(β-D-galactopyranosyloxy)phenyl](pyridin-2-yl)-methyl-1,4,7-triazacyclononane (7): Hexaamine **6** (124 mg, 0.15 mmol) in MeOH (2 mL) was treated with NaOMe (9 mg, 0.15 mmol) under argon. LCMS monitoring indicated that the reaction was complete after 4 h. The solvent was then evaporated and the remaining residue treated with $CHCl_3$ (2 mL) causing a precipitate to form, which was filtered and washed with $CHCl_3$. The combined organic phases were then evaporated to yield **7** (78 mg, 79%). For LCMS purity analysis, see Supporting Information.

Complex 1: A solution of **6** (139 mg, 0.21 mmol) in degassed MeOH (0.15 mL) was treated via cannula and under argon with a solution of $Fe(BF_4)_2{\cdot}6H_2O$ (68 mg, 0.18 mmol) in degassed MeOH (1 mL). A dark brown color appears instantaneously, and the mixture was then stirred for another 10 min before the solvent was fully evaporated. The remaining residue was taken up in a minimal amount of pure water and filtered through a RP-C18 cartridge using water as the eluent. Lyophilization of the fractions containing the product as detected by LCMS yielded **1** as a yellow solid (103 mg, 65%). ^{1}H NMR (200 MHz, D_2O): δ = 7.34–7.95 (m, 19 H), 5.21 (m, 2 H), 4.50–5.00 (m), 4.22–4.43 (m, 1 H), 2.32–4.05 (m, 12 H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 166.0, 165.5, 165.3, 157.4, 154.7, 154.3, 154.2, 137.2, 136.8, 134.3, 132.3, 125.3, 125.1, 125.0, 122.4, 116.5, 116.1, 100.0, 75.3, 75.0, 72.1, 70.1, 68.0, 66.3, 65.9, 62.7, 61.3, 60.3, 58.9, 58.4, 51.9 ppm.

Enzyme Assay Conditions: Phosphate buffer at pH = 7.3 + EDTA [1 mM]; 35 °C; substrate concentration: 1 mg/mL; total volume = 1 mL; addition of 50-μL enzyme stock solution at 1UE/μL.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR, ^{13}C NMR, and ^{13}C NMR DEPT 135 spectra for compounds **1** and **6**; LCMS characterization of compounds **1** and **7**; LCMS monitoring of the two enzyme assays.

Acknowledgments

Financial support from the CNRS, the French Ministry of Research, the Rhone-Alpes Genopole, and Eumorphia are gratefully acknowledged.

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Received: April 24, 2008
Published Online: July 25, 2008

