Organic Process Research & Development **2008,** *12,* 96–100

Implementation on Pilot-Plant Scale of the Titanocene-Catalyzed Reduction of a Lactone with Poly(methylhydrosiloxane)

Dominique Depré,*[,†] András Horváth,[†] Walter Snissaert,[‡] Leo Van Den Bergh,[‡] and Wim Dermaut[§]

Johnson and Johnson Pharmaceutical Research and Development, a Division of Janssen Pharmaceutica, API Development, Turnhoutseweg 30, B-2340 Beerse, Belgium

Abstract:

The titanocene-catalyzed reduction of the lactone 1 into the lactol 2 was studied. This process uses poly(methylhydrosiloxane) as stoichiometric reductant. Thermodynamic and safety data was collected in order to develop a reliable, safe and scalable process that was successfully implemented in the pilot plant. Using this new process, the target lactol was obtained on 30-kg scale with better yield and purity than with a former process using DIBALH, while decreasing the amount of waste.

Introduction

The selective reduction of esters and lactones into aldehydes or acetals and lactols, respectively, is often a challenging reaction and requires generally the use of diisobutylaluminum hydride (DIBALH) in a nonchelating solvent, generally dichloromethane (DCM). Any alternative method to achieve this goal in a practical manner, without using pyrophoric reagents and environmentally problematic solvents, should deserve the consideration of the process chemists.

In this article, we would like to report the development of a safe and scalable process for the selective reduction of the lactone **1** into the corresponding lactol **2** using poly(methylhydrosiloxane) (PMHS) as the stoichiometric reducing agent.

As part of a project on Selective Estrogen Receptor Modulators (SERMs), several batches of RWJ-443931 (Figure 1) were needed for toxicological and clinical studies.[1] The synthesis of this drug substance required the reduction of the lactone **1** into the lactol **2**. For the synthesis of the non-GMP batch and of the first GMP batch, the reduction was performed using DIBALH in dichloromethane (Scheme 1).

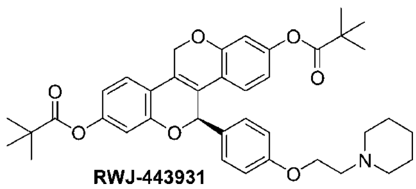
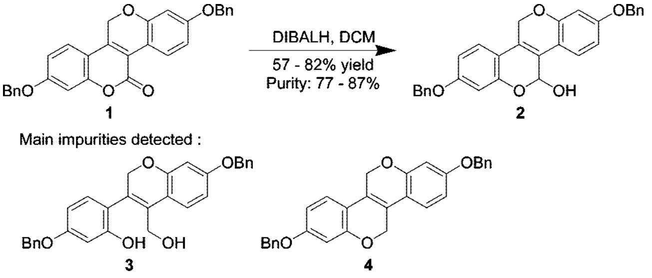

RWJ-443931

Figure 1. **Structure of RWJ-443931.**

Scheme 1



After optimization of the reaction conditions and the workup, compound **2** could be obtained in fair yield and purity. However, this process presented several drawbacks. First, the use of pyrophoric DIBALH together with large amounts of DCM was necessary, which led to high peak volume (up to 15 L/mol **1**) and produced a large amount of waste (60−90 kg waste per kg lactol **2**). Also, the quantity of DIBALH had to be precisely controlled in order to maximize the conversion of **1** and to avoid the over-reduction of **2** into the diol **3** and/or the ether **4**. Finally, the presence of traces of aluminium salts in the isolated lactol **2** led to the formation of undesired side products in the following step of the API synthesis.

Results and Discussion

Screening of Reducing Agents. To improve the synthesis of the desired lactol **2** and to reduce the environmental impact of our processes, we screened several reducing agents (Table 1) and first focused our efforts on the morpholine-modified Red-Al system described in the literature as a possible alternative to DIBALH.[2] However, no selectivity in the reduction could be observed in our case, and even with only 1 equiv of reducing agent, substantial amounts of diol **3** and of several unknown degradation products were produced beside the desired lactol **2** while **1** was still present (entry 1).

We then turned our attention to some catalytic hydrosilylation systems, hoping that more selectivity could be observed. The triethylsilane−ruthenium catalyst combination in refluxing toluene gave no reaction, presumably due to the very low solubility of the starting material in this solvent (entry 2).[3] Changing the solvent from toluene to THF and/or using more active silanes such as phenylsilane or PMHS led either to almost no reaction or to degradation (entries 3–5). Using Mimoun's hydrosilylation system[4] was also unsuccessful in our case, giving only slow degradation of the starting lactone without yielding

---

[*] To whom correspondence should be addressed. E-mail: ddepre@prdbe.jnj.com.

[†] Process Research.

[‡] Pilot Plant.

[§] Safety Testing Laboratory.

(1) (a) Kanojia, R. M.; Jain, N. F.; NG, R.; Sui, Z.; Xu, J. Patent WO 03/053977 A1. (b) Jain, N.; Kanojia, R. M.; Xu, J.; Jian-Zhong, G.; Pacia, E.; Lai, M.-T.; Du, F.; Musto, A.; Allan, G.; Hahn, D. W.; Lundeen, S.; Sui, Z. *J. Med. Chem.* **2006**, *49*, 3056.

(2) Kanazawa, R.; Tokoyorama, T. *Synthesis* **1976**, 526.

(3) Igarashi, M.; Mizuno, R.; Fuchikami, T. *Tetrahedron Lett.* **2001**, *42*, 2149.

(4) (a) Mimoun, H. *J. Org. Chem.* **1999**, *64*, 2582. (b) Mimoun, H. Patent WO 96/12694, 1995.

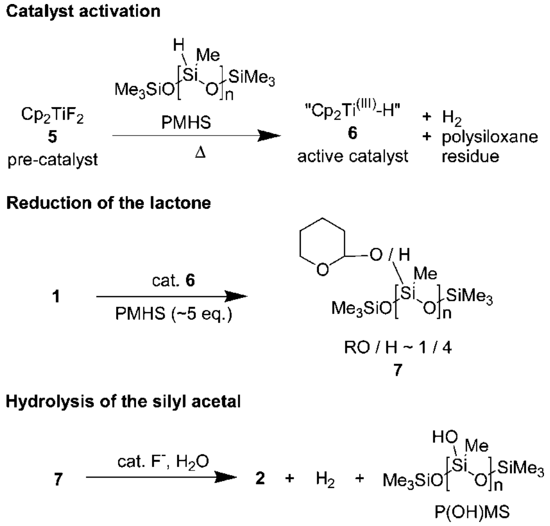
10.1021/op700207m CCC: $40.75

Table 1. **Screening of reducing agents**

entry	conditions[a]	LC (UV 254 nm, area %) 1	2	3	sum other impurities
1	1.2 equiv Red-Al + 1.1 equiv morpholine (premixed), toluene−DCM, 0–5 °C	10.1	14.2	7.4	68.3
2	1.5 equiv Et_3SiH, 0.33 mol % $Ru_3(CO)_{12}$, toluene, Δ	100	0	0	0
3	1.5 equiv Et_3SiH, 0.33 mol % $Ru_3(CO)_{12}$, THF, Δ	94.3	<1.0	0	4.7
4	1.5 equiv $PhSiH_3$, 0.33 mol % $Ru_3(CO)_{12}$, THF, Δ	80.0	2.9	0	17.1
5	~5 equiv PMHS,[b] 0.33 mol % $Ru_3(CO)_{12}$, THF, Δ	50.8	4.5	0	44.7
6	~1.1 equiv PMHS,[b] 5 mol % Et_2Zn-eda, THF, Δ	81.0	0	0	19.0
7	~1.1−5 equiv PMHS,[b] 5 mol % $Zn(EH)_2$, 5 mol % $NaBH_4$, DIPE, Δ	96.8	0	0	3.2
8	3 equiv $PhSiH_3$, 5 mol % Cp_2TiF_2, THF, Δ	1.0	>85.0	0	<15.0
9	5 equiv PMHS,[b] 5 mol % Cp_2TiF_2, THF, Δ	<0.2	>93.0	0	<6.8

[a] Reactions performed on 2.5−5 mmol of starting material. [b] Equivalents of active hydrosiloxane relative to **1** (assuming a mass of 60.13 per siloxane unit).

Scheme 2



any desired lactol (entries 6 and 7). Finally, the titanocene-catalyzed hydrosilylation described by Buchwald et al. allowed us to reduce cleanly **1** into **2** with no or very little over-reduction, even with a large excess (3−5 equiv) of reducing agent (entries 8 and 9).[5,6] Both phenylsilane and PMHS could be used in this process, but being a much cheaper and safer reagent and leading to the formation of less impurities (entries 9 versus 8), PMHS was chosen for further development of the process.[7]

Though the desired reduction was successfully performed on small scale under these conditions, limitations in term of processability were found for several steps of the process (Scheme 2; the structures of **1** and **2** have been simplified in the scheme for clarity).

Indeed, while repeating the activation step on laboratory-scale following the procedure described in the literature (“heat briefly a mixture of titanocene difluoride and PMHS then cool fast to room temperature immediately after the activation occurs”), we noticed a few times an induction period of up to 20 min before the catalyst got activated. This activation was accompanied as described by a sudden evolution of hydrogen and serious foaming, and unlike as described in the literature, the activated catalyst was found to be rather air- and moisture-sensitive and had to be used as soon as possible after activation.[8]

Also, due to the low solubility of the lactone **1** in any suitable solvent at room temperature, the reaction was very slow and deactivation of the catalyst occurred before the end of the reaction, leading to incomplete reduction of **1**. Heating the reaction mixture to reflux solved the problem of solubility and resulted in complete reduction but brought several safety issues that had to be evaluated.

Finally, a large amount of hydrogen gas evolved during the hydrolytic workup and the poly(hydroxymethylsiloxane) byproduct (P(OH)MS) was formed as a partially insoluble and nonfilterable gel beside the desired lactol **2**, making the removal of the byproduct difficult.

In order to make a safe and reliable process on large scale, we studied separately the different steps of the reaction, which are the activation of the catalyst, the catalytic cycle (equal to the reduction of the lactone itself), the hydrolysis of the intermediary silyl acetal **7** yielding the free lactol **2**, and the removal of the polysiloxane byproduct.

Catalyst-Activation Step. We first estimated the lowest activation temperature and the heat generated. A suspension of titanocene difluoride **5** in THF containing enough PMHS to ensure the complete activation of the catalyst was placed in a calorimetric bomb, and the system was stepwise heated until the activation occurred (Figure 2). The activation occurred suddenly after 20 min at 60 °C, generating an adiabatic temperature rise of 5 °C that corresponds to a heat release of ~122.5 kJ/mol **5**, and the pressure rose to almost 5 bar in a few seconds. The maximal temperature and pressure rates were

---

(5) (a) Verdaguer, X.; Berk, S. C.; Buchwald, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 12641. (b) Verdaguer, X.; Hansen, M. C.; Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 8522.

(6) In fact, an excess of PMHS was necessary to perform the complete conversion of **1** into **2**. Using less silane led to incomplete conversion. This was already observed by the group of Buchwald and attributed to some steric hindrance by the reduction product fixed on the polysiloxane chain.

(7) For comparison, the prices for phenylsilane and PMHS were about 166 €/25 g and 35 €/250 g (2007 Aldrich catalogue) whilst the flash points were 7°C and 121°C respectively (Aldrich MSDS).

(8) A few experiments conducted in collaboration with Markó’s group at the Université catholique de Louvain for the reduction of other substrates showed that the stability of the activated catalyst was in fact improved in the presence of hydrogen and that flushing continuously the reactor with nitrogen or argon after the catalyst got activated was detrimental for its stability. We assume that the described stability of the catalyst came from the fact that residual hydrogen gas was left in the flask during the experiments performed S. Buchwald et al.

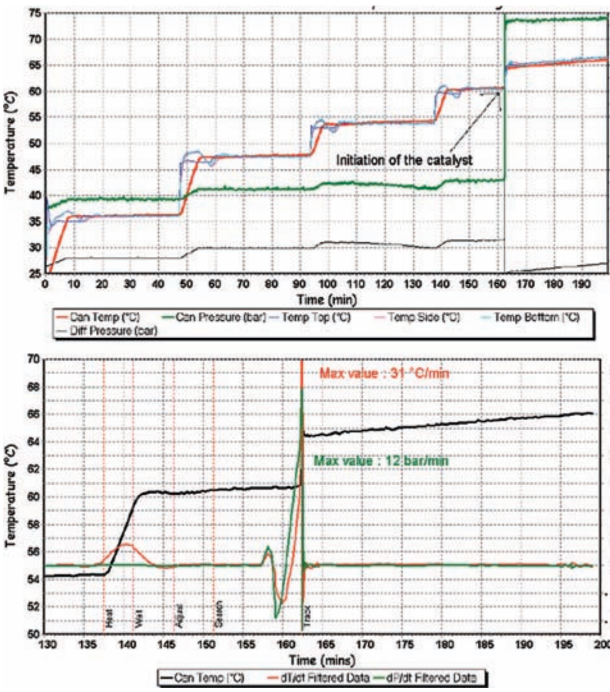


Figure 2. **Temperature and pressure profiles (upper) and temperature and pressure rate profiles (lower) during the catalyst activation (1.08 g 5, 0.3 mL PMHS, 50 mL THF, estimated specific heat 82.8 J/°C, *φ* factor 1.48).**

estimated to 31 °C/min (∼127.3 kW/mol **5**) and 12 bar/min, respectively.

Assuming that working at higher temperature would reduce the induction time before activation and slowly adding the PMHS would reduce the sudden temperature and pressure rise as well as the serious foaming, we suspended **5** in toluene under nitrogen and heated the suspension to 90–100 °C before adding slowly only a slight excess to the necessary quantity of PMHS for the activation (∼2 equiv relative to **5**).[9]

Under those conditions, the activation became virtually immediate, and as a result of the slow addition of the silane, the evolution of hydrogen became controllable. Furthermore, at 90 °C, the siloxane byproduct reticulated fast to yield a powder that did not stick to the reactor wall. Working below the reflux temperature of the solvent, the foaming was also dramatically reduced though not totally suppressed.[10]

After the addition of PMHS, the reaction mixture was cooled to 50–60 °C, and THF was added to get an homogeneous mixture. This way, **5** was smoothly converted to a dark blue solution of activated catalyst **6**. This solution was kept under nitrogen and used as soon as possible for the reduction of the lactone.[11]

Reduction Step. The reduction of the lactone was found to be only slightly exothermic, and almost no formation of gas or foaming was observed. Nevertheless, as already mentioned, the solubility of **1** in the reaction solvent was very low at room temperature, and long reaction times and partial deactivation of the catalyst were observed. Suspending **1** and 4–5 equiv of PMHS in THF at 45–50 °C and then adding the solution of

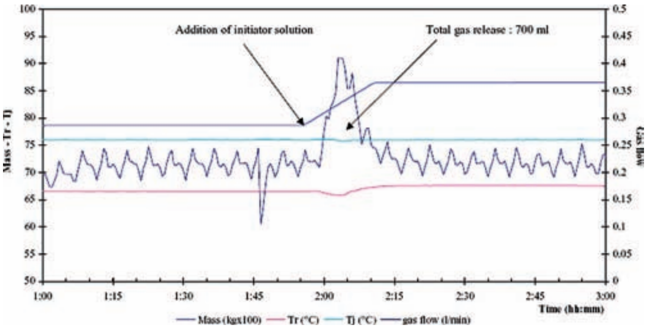
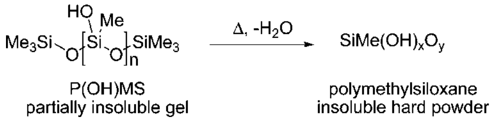


Figure 3. **Temperature profile and gas evolution during the addition of the activated catalyst 6 to the hot suspension of 1 and PMHS (78 mL solution of 6 added over 15 min to 69.4 g 1, 50 mL PMHS and 750 mL THF under a constant nitrogen flow of 0.2 L/min).**

Scheme 3



catalyst allowed us to reach a complete conversion after 3 h of reflux without safety issues. As shown in an experiment conducted in an RC-1 reactor (Figure 3), limited gas evolution (700 mL) could be observed on 0.2 mol **1** scale.

Hydrolysis of Silyl Acetal 7 and Removal of Siloxane Byproduct. The hydrolysis step performed in a RC-1 reactor was found to be strongly exothermic (269 kJ/mol **1**), and as a result of the necessary excess of PMHS,[6] a large amount of hydrogen was formed (140 L/mol **1**). Furthermore, some foaming occurred when the hydrolysis was carried out at reflux.

The heat release and gas formation were made controllable and foaming was avoided by adding slowly a solution of 5 mol % tetrabutylammonium fluoride (TBAF) and ∼10 equiv water in THF to the reaction mixture kept at 45–50 °C.

To ensure a complete liberation of **2** from the silyl acetal **7** and to get easily filterable byproduct, Dicalite was added and the reaction mixture was refluxed for 5−15 h after the addition of the quenching solution. This prolonged heating period together with the presence of Dicalite allowed the polysiloxane to dehydrate and to reticulate into an insoluble hard powder (Scheme 3). The byproducts were then easily filtered off from the reaction mixture, and the desired lactol **2** was isolated in an active yield of up to 83% and in up to 93% purity from the filtrate after a solvent switch to toluene then to ethanol and filtration.

Transfer of the Process to Pilot-Plant Scale. A test of the so-designed process was carried out twice on 70-g scale in standard laboratory glassware and allowed us to obtain the desired lactol **2** in a 78–83% active yield and with a constant

---

(9) Other high-boiling solvents like 1,2-dimethoxyethane or dioxane should be also suitable solvents for the activation step.

(10) Due to the foaming, we recommend not to fill the reactor more than 50% capacity during the activation step.

(11) Though the catalyst was described as water- and air-stable (see ref 5), a partial deactivation was sometimes observed on standing when the experiment was performed on small scale, resulting in a colour change from dark blue to greenish. The use of this deactivated catalyst in the reduction step led to serious foaming, probably due to reactivation of the catalyst and concomitant hydrogen evolution. The deactivation was found to be due to accidental exposure with air, and the stability of the catalyst was strongly improved when kept under hydrogen (see note 8). This deactivation of the catalyst was nevertheless not observed on scale.

Table 2. **Reduction process on pilot-plant scale**

batch	scale (kg **1**)	**2** obtained (kg)	% yield (active)	purity (wt %)
1	0.069	0.063	84	92
2	10.0	7.2	63[a]	87
3	30.3	34.6	81	71[b]
4	30.2	25.0	76	92
5	29.4	29.4	78	88

[a] Some lactol **2** was kept entrapped in the polysiloxane matrix on the surface of the reactor. [b] Due to insufficient removal of siloxane byproduct.

Table 3. **Comparison of DIBALH and PMHS processes**

	DIBALH process	PMHS process
active yield (%)	57–82	76–84
purity (wt %)	77–87	71–92
waste (kg/kg **2**)		
salty WL	24–35	none
solvents	39–56	26–30
H_2	none	<0.2
polysiloxane	none	<1
total	63–90	27–31
yield of following intermediate	33–70	60–71

purity of 93% without problem. The process was then performed again without safety issue on 10-kg scale and then three times on 30-kg scale in stainless steel reactors, giving **2** in similar yield and purity as on smaller scale (Table 2). We must point out that a suitable heating system that avoids overheated zones on the surface of the reactor is necessary. Indeed, heating the reactor with pressurized steam as for the batches 2 and 3 was the origin of hot spots on the surface of the reactor and led to the precipitation of the siloxane byproduct on the wall of the reactor and of the formation of a crusty ring at the level of the interface between the reaction mixture and the vapour phase. Controlled smooth heating avoided the formation of this crust and **2** was isolated in constant yield and purity similar to that on small scale (Table 2). Furthermore, the absence of traces of aluminum species in **2** allowed us to perform the following step in the synthesis of RWJ-443931 and to isolate the corresponding intermediate in more consistent yield (60–71% yield versus 33–70%; Table 3).

Conclusion

After thermodynamic studies and safety data collection, we could develop a new process for the reduction of the lactone **1** into the lactol **2** and successfully implemented it on up to 30-kg scale in our Pilot-Plant facilities. This process uses titanocene species as catalyst and the cheap and easy-to-handle poly(methylhydrosiloxane) as stoichiometric reducing agent. This new process allowed us to replace a less environmentally friendly procedure using DIBALH and DCM and led to the formation of the desired lactol in higher yield and purity while reducing drastically the amount of waste.

Experimental Section

All small-scale experiments were carried out using standard laboratory glassware, and the experiments on scale were carried out in stainless steel reactors. The reagents and solvents were standard technical-grade and were used without any purification. PMHS was purchased from Bayer General Electric (Baysilone MH 15). Titanocene difluoride was synthesized from titanocene dichloride according to a literature method.[12]

HPLC analyses were performed on reversed-phase columns (C18) in gradient mode (ammonium acetate buffer to acetonitrile) with UV detection (254 nm). NMR spectra were recorded on a Bruker AV 400 instrument. LC-MS analyses were performed on a Micromass platform LCZ.

2,8-Bis(benzyloxy)-5,11-dihydrochromeno[4,3-*c*]chromen-5-ol (2). A 50-L stainless steel reactor (reactor 1) was inerted with nitrogen and then charged with 686 g (3.18 mol) of titanocene difluoride and 15.9 L of toluene. The suspension was stirred and heated to slightly below the reflux temperature (100 °C), and then 1.27 kg (21.1 mol active hydrosiloxane) of PMHS previously dissolved in 2.9 L of toluene was added in such a way that the hydrogen evolution and foaming were kept under control (addition over 15 min). The beginning of the activation was clearly visible as evidenced by a darkening of the suspension.[13] The suspension was then cooled to 60 °C, and 15.9 L of THF was added to get a dark blue solution of active catalyst. This solution was kept under inert atmosphere before its transfer into the reactor containing the lactone **1** and PMHS. A 500-L reactor (reactor 2) was inerted with nitrogen and then charged with 29.37 kg (63.5 mol) of lactone **1**, 20.96 L (348.6 mol active hydrosiloxane) of PMHS and 286 L of THF. The suspension was stirred and heated to 55–60 °C. The solution of active catalyst was transferred from reactor 1 into reactor 2 (addition over 15 min) and then the reactor 1 was rinsed with 8.8 L of THF, also transferred into reactor 2. The suspension in reactor 2 was stirred at reflux (65–67 °C) for 3 h to ensure a complete conversion of the starting lactone **1**; the reaction mixture became then a solution. The temperature of the reaction mixture was set to 50–55 °C before the quenching solution was added. Reactor 1 was again charged with 8.3 L of water, 3.18 L of 1 M tetrabutylammonium fluoride (TBAF) solution in THF and 82.5 L of THF. This quenching solution was added into reactor 2 in such a way that the gas evolution and potential foaming were kept under control (addition over 60–80 min with the first 30 L added over 30 min). After complete addition of the quenching solution, the reaction mixture was refluxed overnight (reflux temperature, 65 °C) and then cooled to room temperature, charged with 2.9 kg of Dicalite, stirred for 30 min and filtered. The insoluble materials containing the polysiloxane byproduct were washed with 25.4 L of THF and then discarded. The filtrate and the washing fraction were combined and brought back in reactor 2. Then 300 L of the solvent was distilled (solution temperature, 65–72 °C), 95.3 L of toluene was added and an additional 120 L of solvent was distilled. The temperature of the distillate reached 105–110 °C at the end of the distillation. The content of the reactor was cooled to 70 °C, and 127 L of ethanol was added to precipitate the lactol **2**. The suspension was cooled to room temperature and further stirred

---

(12) Druce, P. M.; Kingston, B. M.; Lappert, M. F.; Spalding, T. R.; Srivastava, R. C. *J. Chem. Soc. A* **1969**, 2106.

(13) Though we did not confirm the activation of the catalyst other than by the colour change, the activation point can be also detected by measuring the gas evolution and, due to the high exothermicity of the activation, by measuring the heat flows between the reaction mixture and the reactor mantle.

during 1 h before the lactol **2** was filtered, washed with 25.4 L of ethanol and dried overnight at 50 °C under vacuum. 26.1 kg of **2** were obtained as an off-white powder. LC assay: 88%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.07 (dd, J = 14.4, 1.0 Hz, 1 H), 5.10 (s, 2 H), 5.13 (s, 2 H), 5.21 (d, J = 14.4 Hz, 1 H), 6.31 (d, J = 6.8 Hz, 1 H), 6.56 (d, J = 2.5 Hz, 1 H), 6.64 (dd, J = 8.6, 2.5 Hz, 1 H), 6.67 (s, 1 H), 6.68 (dd, J = 8.1, 2.5 Hz, 1 H), 7.18 (m, 1 H), 7.20 (d, J = 8.6 Hz, 1 H), 7.28 (d, J = 7.1 Hz, 1 H), 7.30−7.35 (m, 2 H), 7.37–7.41 (m, 4 H), 7.42–7.47 (m, 4 H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 63.53, 69.29, 69.33, 88.39, 102.63, 103.22, 108.20, 108.28, 112.05, 113.69, 118.44, 119.00, 123.25, 123.55, 127.60, 127.81, 128.41, 136.91, 151.76, 154.33, 158.90, 159.09. LC-MS (ESI) m/z (+): 447.16 ([M − OH]$^+$); (−): 463.14 ([M − H]$^-$), 927.40 ([2M − H]$^-$). High resolution mass confirms the elemental composition.

Received for review September 6, 2007.

OP700207M