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Study of the O-glycidylation of natural phenolic compounds. The relationship between the phenolic structure and the reaction mechanism

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ABSTRACT

The O-alkylation reaction by epichlorohydrin of some natural phenolic compounds such as 4-methylcatechol, gallic acid, protocatechuic acid, pyrogallol and resorcinol was investigated. Phenolic compounds reacted first with epichlorohydrin in the presence of benzyltriethylammonium chloride as phase transfer catalyst. Then, an aqueous solution of sodium hydroxide was added.
It was demonstrated that the two competitive mechanisms involved in the O-alkylation reaction were highly dependent of the starting material. The *O*-alkylated products obtained in this reaction could be further used as bisphenol A substitutes in the synthesis of epoxy resins pre-polymers.

1. Introduction

Bio-based polymer products derived from annually renewable agricultural and biomass feedstock have become increasingly important as sustainable and eco-efficient products, which will potentially replace the products based exclusively on petroleum feedstock.[1,2] Of all polymers produced, the thermosets represent an important class in the industry due to their high flexibility for tailoring desired ultimate properties, leading to their high modulus, strength, durability, and thermal and chemical resistances as provided by high cross-linking density.[3–7] Paradoxically, thermosets prepared from renewable resources have been the subject of limited investigations.[8]

Epoxy resins are some of the most important thermosetting resins, and are extensively used as coatings, adhesives, electronic materials, and for structural applications because of their outstanding mechanical properties ranging from extreme flexibility to high strength and hardness, high adhesion strength, good heat resistance and high electrical resistance.[9,10] Nowadays, almost 90% of the world production of epoxy resins is based on the reaction between bisphenol A (BPA) and epichlorohydrin, yielding diglycidyl ether of bisphenol A (DGEBA). Suspected of being hazardous to humans, concerns about the use of BPA in consumer products have been regularly reported in the news media since 2008 after several scientists and governments questioned its safety.[11–14] Therefore, there is a huge interest in developing a bio-based epoxy monomer or oligomer able to replace the traditional DGEBA by offering high performance materials.

In the manufacturing of sustainable epoxy resins, epoxidized plant oils (soybean oil, linseed oil, castor oil…) and fatty acids have been largely utilized as reported in the literature.[15–17]

However, these networks present disadvantages in heat resistance and mechanical properties due to the long aliphatic chains. Thus, this type of epoxy resin is applied only in limited fields of applications. Recently, the use of natural polysaccharides in the synthesis of bio-based epoxy resins retained industrial and scientific interest. Indeed, the conversion of maltitol, and sorbitol into multifunctional epoxy monomers has been reported.[18] Glycerol polyglycidyl ether, usually employed in textile and paper as processing agent and as reactive diluent, was reacted with curing agent to produce bio-based epoxy resin.[19] Isosorbide produced from the double dehydration of sorbitol was also used as a substitute of bisphenol A to produce epoxy material with good network properties.[20,21] Unfortunately, glycidyl ether derivatives of

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polysaccharide monomers are hygroscopic and the presence of water may deteriorate the properties of the networks.

The heat resistance and the mechanical and electrical performance properties of organic compounds are generally attributed to the aromatic ring structure. Most of the naturally occurring aromatic compounds are often believed to be originated from lignin. For this reason, many researchers have made their efforts to apply these macromolecular compounds to the production of epoxy resins. Until now, methods to synthesize lignin-based epoxy resin can be summarized into two categories as follows: (i) blending derivatives of lignin with epoxy resin directly;[22] (ii) modifying lignin derivatives (organosolv lignin) to improve their reactional ability, followed by epoxidation.[23,24] However, all lignins created problems with organic solvent—solubility, and thus required special solvent mixtures for formulation. Moreover their chemical structures, which are not yet entirely elucidated, could make the direct functionalization of this polymer difficult.

The other terrestrial source of phenolic compounds is tannins. Tannins are defined as water-soluble plant phenolic compounds having molecular weight ranging from 500 Da to 3000–4000 Da. Furthermore, the compounds should undergo the usual phenolic reactions and have the ability to precipitate some alkaloids, gelatin and other proteins from solutions.[25–27] They constitute an important group within the phenolic compounds and may be subdivided into hydrolyzable and condensed tannins. The former are esters of gallic acid (gallo- and ellagitannins), while the later (also known as proanthocyanidins) are polymers of polyhydroxyflavan-3-ol monomers. Another subdivision, the phlorotannins derived from the oligomerizing dehydrogenative coupling of phloroglucinol, have been isolated from several genera of red-brown algae.[26,28–30] Thus, tannins exhibit a wide structural diversity and their molecular structure is a key determinant of their chemical reactivity.

The objective of our ongoing research is to study the feasibility of replacing bisphenol A by such natural phenolic compounds in the synthesis of novel bio-based reactive pre-polymer systems.

In our previous paper,[31] one of the building blocks of polymeric condensed tannins, namely catechin, was reacted with epichlorohydrin in alkaline medium to lead to the expected tetraglycidylether of catechin along with a benzodioxane derivative (Scheme 1). The formation of this cyclic by-product seemed to be directly related to the *ortho*-positions of the two phenolic OH groups carried by the B-ring of catechin.[31]

In 1985, the glycidylation of gallic acid (building block of gallotannins) had been claimed in a patent from Haruo Tomita et al.[32] The use of a phase transfer catalyst (PTC) and a two step-procedure in Tomita's protocol make the noticeable differences compared to the protocol that we used for the catechin glycidylation. The O-alkylation product obtained by the experimental conditions given in the patent is reported as being the product of substitution reaction of epichlorohydrin onto the carboxyl group and at least onto one phenolic hydroxyl group. The formation of side-products such as the benzodioxane derivative that we obtained with catechin was not mentioned in this work in spite of the presence of three hydroxyls groups in *ortho*-position on the aromatic ring of gallic acid.

Although the experimental conditions of the reaction are not totally the same between the work that we reported earlier on catechin and those of the Haruo Tomita's patent on gallic acid, the products obtained after reaction suggest a difference in reactivity between the two phenolic compounds towards epichlorohydrin. Therefore, we decided to investigate further the role of the phase transfer catalyst (PTC) on one hand, and, on the other hand, the glycidylation of model phenolic compounds by epichlorohydrin in order to ultimately optimize the functionalization reactions of natural tannins. For this purpose, some characteristic mononuclear aromatic phenolic compounds, bearing two or three phenolic hydroxyls in *ortho*- or *meta*-positions, with or without additional carboxylic group, were reacted with epichlorohydrin. The structures of the glycidylated products were determined, mainly from NMR experiments. The glycidylation mechanism was then discussed on the basis of the structural characterizations.

The model phenolic compounds studied in the present work are: 4-methylcatechol, gallic acid, protocatechuic acid, pyrogallol and resorcinol.

2. Results and discussion

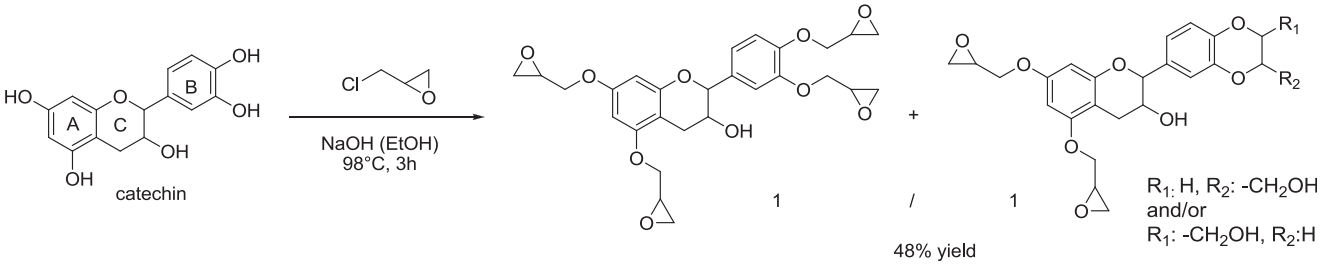
2.1. Confirmation of the benzodioxane structure in the glycidylation of 4-methylcatechol

In our previous work related to the functionalization of catechin,[31] the reaction of 4-methylcatechol **1** (as representative of the B-ring of catechin) with epichlorohydrin in alkaline medium revealed the formation of the benzodioxane derivative **3** besides the expected glycidylation product (Scheme 2). This cyclic by-product was tentatively identified by NMR analyses among a mixture of other impurities.

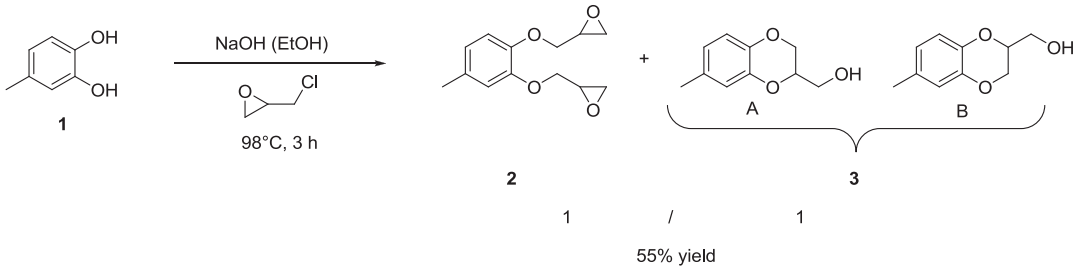
In order to unequivocally establish the chemical structure of the hypothetical benzodioxane derivative, the glycidylation reaction of 4-methylcatechol **1** was repeated in the same reaction conditions mentioned in our anterior work.[31] The crude product was purified by silica gel chromatography allowing the isolation of products **2** and **3** in equal amount. These products definitely correspond, respectively, to the diglycidylether and the benzodioxane derivative of 4-methylcatechol, (Scheme 2).

Detailed structure characterization of product **3** was performed by NMR spectroscopy. The ^{1}H NMR spectrum (Fig. 1) displays resonance signals easily attributed using both their chemical shifts and coupling pattern. The 6.6–6.8 ppm region contains an ABX system corresponding to the **3** aromatic ring protons whereas the aliphatic signals in the 3.5–5.1 ppm range arise from the dioxane group. The dioxane hydroxyl group gives a characteristic signal at 5.03 ppm, the methylene proton Ha and Ha′ resonance signals are located at 3.96 and 4.27 ppm while the signal at 4.09 ppm is assigned to the methyne proton Hb.

The HMBC spectrum of product **3** (Fig. 1) allows to attribute the quaternary carbons of the aromatic ring C1, C2 and C3 from their correlations with both the aromatic, the methyne and the methyl



Scheme 1. Glycidylation of catechin.



Scheme 2. Glycidylation of 4-methylcatechol in the presence of ethanolic solution of NaOH.

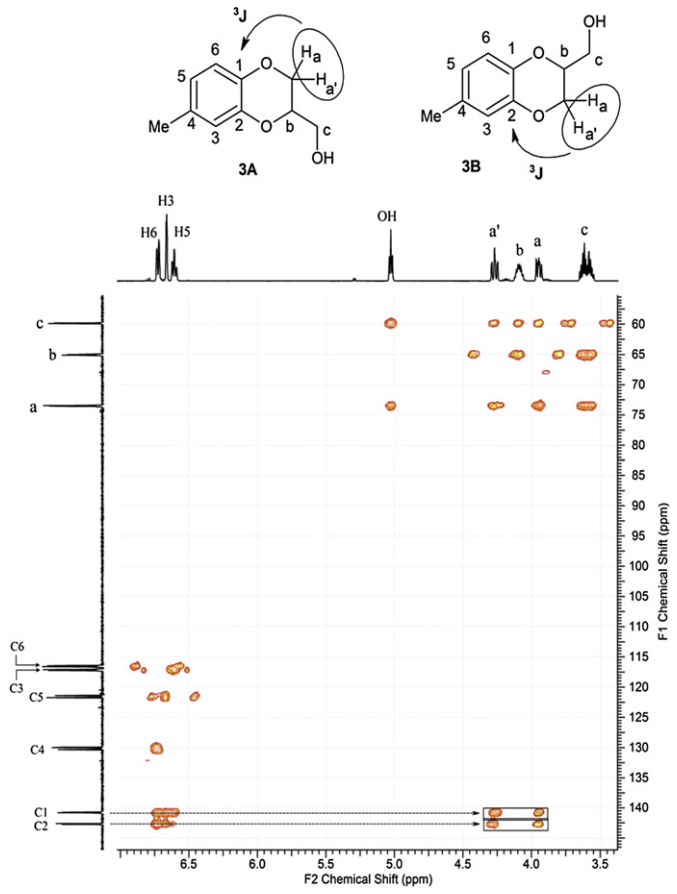


Fig. 1. HMBC spectrum of products **3A** and **3B** in DMSO-d_6 showing the correlations between the methylene protons Ha and Ha′ and the quaternary carbons C1 and C2.

protons. From the intensity of the long-range correlations, it is also possible to demonstrate the presence of two regio-isomers A and B as shown in Scheme 2. The methylene protons Ha and Ha′ give indeed strong correlations with both quaternary carbons C1 and C2. Since the intensity of $^{1}H-^{13}C$ long-range correlations are directly related to the *n*-bond coupling constants for a given proton and a given delay of the HMBC spectrum,[33,34] it means that these cross-peaks correspond both to ^{3}JCH correlations.

2.2. Glycidylation of gallic acid

Gallic acid **4** is a phenolic compound encountered in different plants in various forms, as gallic acid derivatives (esters, glycosides) or as the acyl groups of some polyols (glucose, quinic acid). Some studies have reported the use of this phenolic compound in thermosetting applications, especially as an adjuvant in the epoxy resins curing.[35–37] Only Tomita et al.[32] achieved the O-glycidylation of gallic acid in the presence of PTC. However, the reaction products were poorly characterized and the reactivity of gallic acid was not discussed. Therefore, we carried out the reaction with gallic acid following carefully the experimental procedure disclosed in Tomita's invention. Thus, gallic acid was mixed with epichlorohydrin (molar ratio hydroxyl group/epichlorohydrin, 1:4) in the presence of benzyltriethylammonium chloride ($BnEt_3NCl$) (molar ratio substrate/catalyst, 1:0.05) and the mixture was heated 1 h at 100 °C. Then, the solution was cooled to 30 °C. The previous amount of phase transfer catalyst (PTC) was added again along with an aqueous solution of sodium hydroxide (molar ratio hydroxyl group/NaOH, 1:2). The reaction mixture was further stirred at 30 °C for 90 min. The purification of the crude product by silica gel chromatography allowed the isolation in fair yield (68%) of compound **5** (Scheme 3).

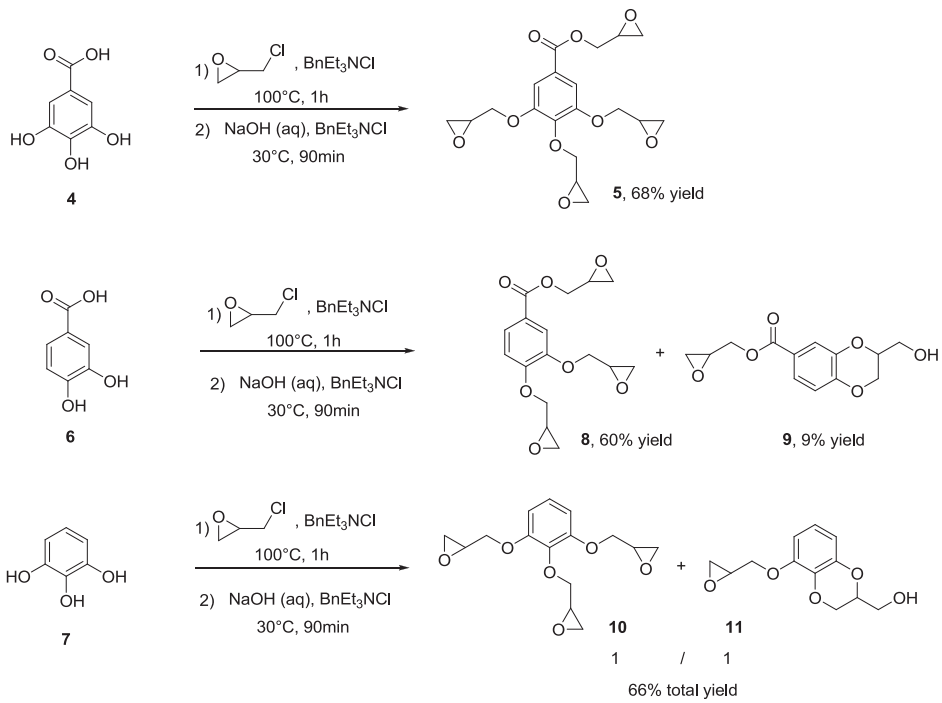
The formation of the tetraglycidylated derivative of gallic acid **5** was established from ^{1}H NMR spectrum (see Experimental section). Whereas the characteristic phenolic and carboxyl hydroxyl proton resonance signals (*at ~9.5 ppm and ~12.5 ppm, respectively*) cannot be observed, numerous aliphatic signals arising from oxirane groups are identified. The methylene and methyne ring proton signals appear in the 2.73–4.65 ppm range and the CH_2–O protons give resonance signals in the 3.92–4.65 ppm spectral range. The average number of oxirane groups per gallic acid ring, calculated from the ratio of ^{1}H surface signal integrations, was equal to ~4. Interestingly, in contrast to what was observed with methylcatechol, no benzodioxane derivative was detected, despite the *ortho*-positions of the three phenolic hydroxyls carried by gallic acid.

It was verified that the formation of benzodioxane derivatives from glycidylation reaction of methylcatechol was not due to differences in reaction conditions, especially the lack of PTC ($BnEt_3NCl$). For this, 4-methylcatechol **1** was reacted with epichlorohydrin in the same experimental conditions than the ones applied to gallic acid (i.e., with PTC). Products **2** and **3** were obtained in equivalent amounts, with a total reaction yield of 67%. Therefore, the use of PTC in glycidylation reaction does not prevent the formation of benzodioxane derivatives. It only increases the reaction yield.

The absence of benzodioxane derivative during the gallic acid glycidylation prompted us to investigate in greater details the source of the difference in reactivity of this phenolic compound towards epichlorohydrin. For this purpose, two phenolic compounds, protocatechuic acid **6** and pyrogallol **7**, whose chemical structures are close to that of gallic acid, were reacted with epichlorohydrin using the procedure described in Scheme 3.

2.3. Glycidylation of protocatechuic acid 6 and pyrogallol 7

The treatment of protocatechuic acid **6** by epichlorohydrin in the presence of $BnEt_3NCl$ as PTC led to the triglycidylated derivative **8** as the main product (60% yield) along with a small amount (9%



Scheme 3. Glycidylation of **4**, **6** and **7** in the presence of PTC followed by basic treatment.

yield) of benzodioxane derivative **9.** The structures of products **8** and **9** were determined by NMR spectroscopy. As explain below for products **3A** and **3B**, the position of the dioxane ring of product **9** was determined from the long range $^{1}H-^{13}C$ correlations, which showed that only one regio-isomer was formed as displayed in Scheme 3.

Similarly, pyrogallol **7** was reacted with epichlorohydrin to give a mixture of two products, which could not be separated. NMR analyses of this mixture revealed the presence of the triglycidylether of pyrogallol **10** and the benzodioxane derivative **11** in equivalent amounts (Scheme 3). NMR data of product **11** showed that only one regio-isomer was formed.

These results suggest that the presence or absence of the carboxyl group on the phenolic compound influences strongly the distribution of the products obtained as demonstrated by the reaction of pyrogallol that lacks this substituent and led to the formation of the benzodioxane derivative, in amounts comparable to those obtained with 4-methylcatechol **1**. In order to better understand the reactivity of these compounds, the glycidylation reaction was investigated step by step.

2.4. Investigation of the glycidylation reaction mechanism

The O-alkylation of alcohols or phenolic compounds in the presence of PTC such as ammonium salt was widely described in the literature.[38–41] Nevertheless, in most studies, the phenolic compound is dissolved in an organic solvent and then an aqueous solution of base such as NaOH is added in the presence of PTC. In this aqueous-organic two-phase system, the reacting nucleophile is provided by the aqueous phase and is usually insoluble or slightly soluble in the organic phase under operating conditions.[41]

In contrast, our glycidylation reaction proceeds in two steps: the first step consists in heating a suspension of solid phenolic compound (nucleophile) and liquid epichlorohydrin (electrophile) at 100 °C in the presence of PTC for 1 h. In the second step, an aqueous solution of NaOH containing PTC is added to the previous reaction medium. In order to clarify the role of the phase transfer catalyst, the glycidylation reaction was carried out with or without $BnEt_3NCl$ and stopped prior to the addition of the base solution.

Thus, gallic acid **4** and epichlorohydrin were mixed in the presence of $BnEt_3NCl$. Initially, the solid gallic acid was observed to be only slightly soluble in epichlorohydrin but after 1 h at 100 °C, a homogenous solution was obtained. After epichlorohydrin evaporation and silica gel filtration, the residue was analysed by NMR spectroscopy, which revealed that products **12a**, **12b** and **12c** were formed (Scheme 4). These products are evidence of the reaction process: a nucleophilic attack of the phenolate ions onto the electrophilic methylene carbon of the epichlorohydrin oxirane, thereby causing the opening of the oxirane ring to occur.

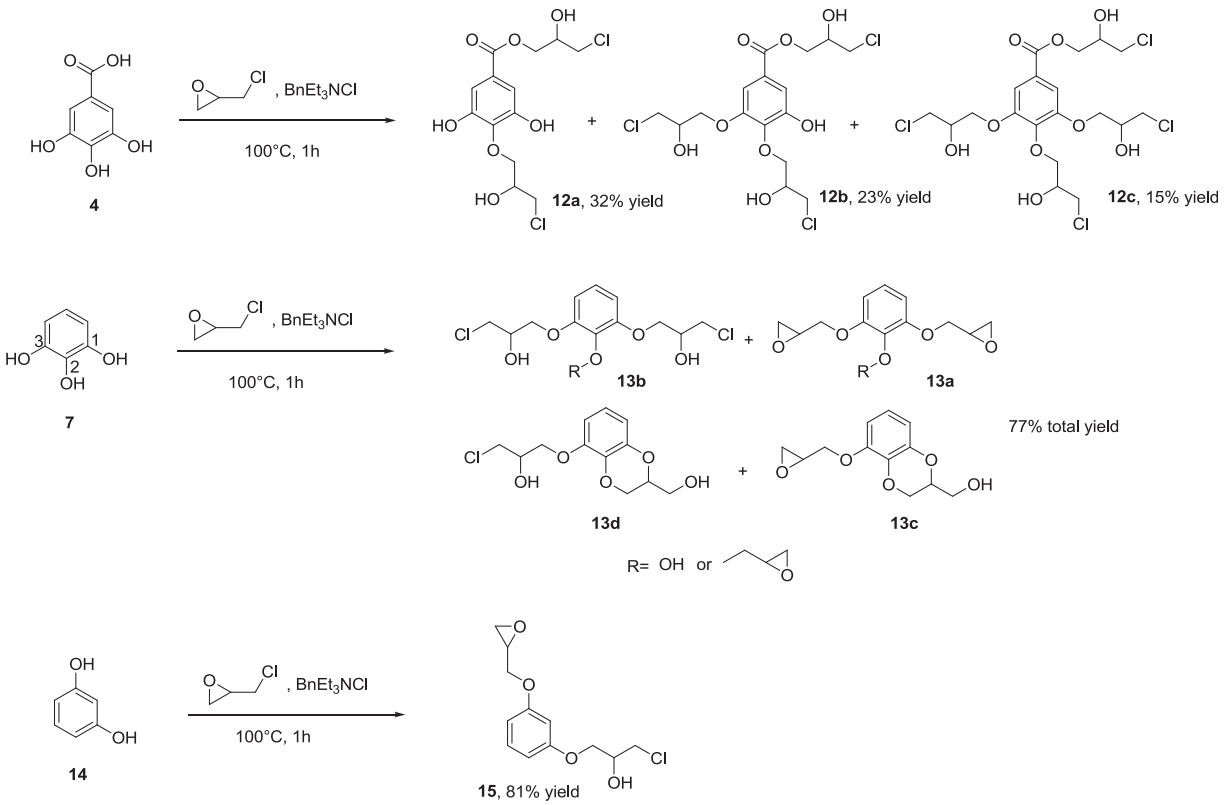
In the absence of $BnEt_3NCl$, the substrate was entirely recovered without any detectable traces of any other products, suggesting complete unreactivity of phenolic compounds with epichlorohydrin in the absence of PTC. These results point out the crucial role of the catalyst in the formation of phenolate ions. This reaction system is called the solid–liquid phase transfer catalysis. Yang and Wu[42] proposed a conceptual scheme describing the reaction mechanism in solid–liquid phases. In their system, *O*-phthalic acid (ArH_2) was reacted with potassium hydroxide (KOH) to produce potassium phthalate ArK_2.

Without the addition of any water, phase transfer catalyst QX can solvate and react with solid ArK_2 to produce ArQ_2 dissolved in organic phase. Then, the active intermediate ArQ_2 (org) reacts with the organic substrate RX to form the desired product ArR_2. This mechanistic model could be applied to our reactional system with the only difference being that gallic acid hydroxyls are able to form ion-pairs with PTC even in absence of base.

The overall reaction of solid gallic acid ArOH and organic epichlorohydrin RX under the action of phase transfer catalyst QX, could be formally expressed as follows:

$$ArOH(sol) + RX(org) + QX(org) \rightarrow ArOR(org) + HX(org) + QX(org)$$

The role of PTC being better clarified, the reaction of pyrogallol **7** with epichlorohydrin and $BnEt_3NCl$ was also performed.



Scheme 4. Reaction of **4**, **7** and **14** with epichlorohydrin in the presence of PTC. Products analyses were done before the addition of the base solution.

A detailed structural characterization of the mixture recovered after 1 h at 100 °C was performed using several NMR spectroscopy experiments (see Experimental section).

The 1D and 2D NMR spectra indicate the presence, in equivalent amount, of two types of molecules, which are different in their aromatic ^{1}H spin systems. For one type of molecules, the aromatic ring displays an AB spin systems (i.e., one triplet and one doublet representing one and two protons, respectively), revealing symmetric aromatic rings whereas the molecules of the other type exhibit ABC spin systems (i.e., three multiplets, each representing one proton), the signature of asymmetric aromatic ring. Besides aromatic protons, NMR spectra show a number of aliphatic ^{1}H and ^{13}C resonance signals. Most of them were assigned from NMR spectra allowing the distinction of three different substituents: oxirane, dioxane and chlorohydrin groups. The linkage position of these groups on the aromatic rings was then determined using $^{1}H-^{13}C$ long range correlations between the $-CH_2-O-$ protons of the substituent groups and quaternary carbons of the aromatic rings as shown in Fig. 2. We thus found that, in symmetric aromatic rings, both hydroxyls 1 and 3 are substituted, by either oxirane or chlorohydrin groups. The hydroxyl 2 position is also partly substituted but only by oxirane group. The asymmetric aromatic rings are characterized by the presence of a dioxane group, linked to two adjacent hydroxyl positions of the phenyl ring. The protons CH_2-O of the dioxane groups give correlations only with C2B (and not C3B) showing that only one regioisomer was formed as displayed in Fig. 2. The third hydroxyl position is substituted by either an oxirane or a chlorohydrin group. These products **13a**–**13d** are shown in Scheme 4 (Fig. 2).

Besides NMR analyses, the kinetics of the pyrogallol O-glycidylation reaction was monitored and products were analysed by a tandem UPLC/ESI-MS in positive mode (Fig. 3).

The three substituents (oxirane, dioxane and chlorohydrin) identified by NMR analyses, successively appeared in the reaction medium beginning by the methylchlorohydrin derivative (m/z 219 and 311). The abundant ion at m/z 275, which occurred after 30 min reveals that the production of the benzodioxane derivative requires more time. The substitution of phenolic hydroxyl proton by a methyloxirane group (m/z 389) was observed at the end of the reaction (Fig. 3).

According to these results, we noticed that the number and the nature of substituents on the phenyl ring influence the reactivity of phenolic compounds towards epichlorohydrin and the regio-selectivity of this reaction. For this reason, the O-glycidylation reaction of resorcinol **14**, which possesses two phenolic hydroxyl groups at *meta* position from each other was studied. Applying the same experimental procedure used for gallic acid and pyrogallol, the reaction of resorcinol with epichlorohydrin in the presence of PTC led to product **15** in 81% yield (Scheme 4).

Although the phenolic hydroxyls of resorcinol are equivalent, they react in different way towards epichlorohydrin (two different substituents). This result proves unequivocally that, in reaction mixture, a permanent competition exists between two different mechanisms (Scheme 5). In the mechanism A, the direct nucleophilic substitution (S_N2) of phenolate ion (ArO^-) on epichlorohydrin occurs, concomitantly with the cleavage of C–Cl bond. In the mechanism B, the attack of ArO^- causes the opening of epichlorohydrin ring followed by the protonation of the resulting alcoholate **16** formed in situ. Thus, both mechanisms A and B are involved in the glycidylation reaction of resorcinol and pyrogallol. However, only methylchlorohydrin derivatives (**12a**–**12c**) have been generated by the reaction of gallic acid with epichlorohydrin revealing the prevalence of mechanism B in this case.

From gallic acid, the mixture obtained (**12a**–**12c**) indicates that the glycidylation occurred first in carboxylic function, which is transformed into ester.

Thus, we can deduce that the presence of this electron-withdrawing group on phenolic ring may promote mechanism B (Scheme 5).

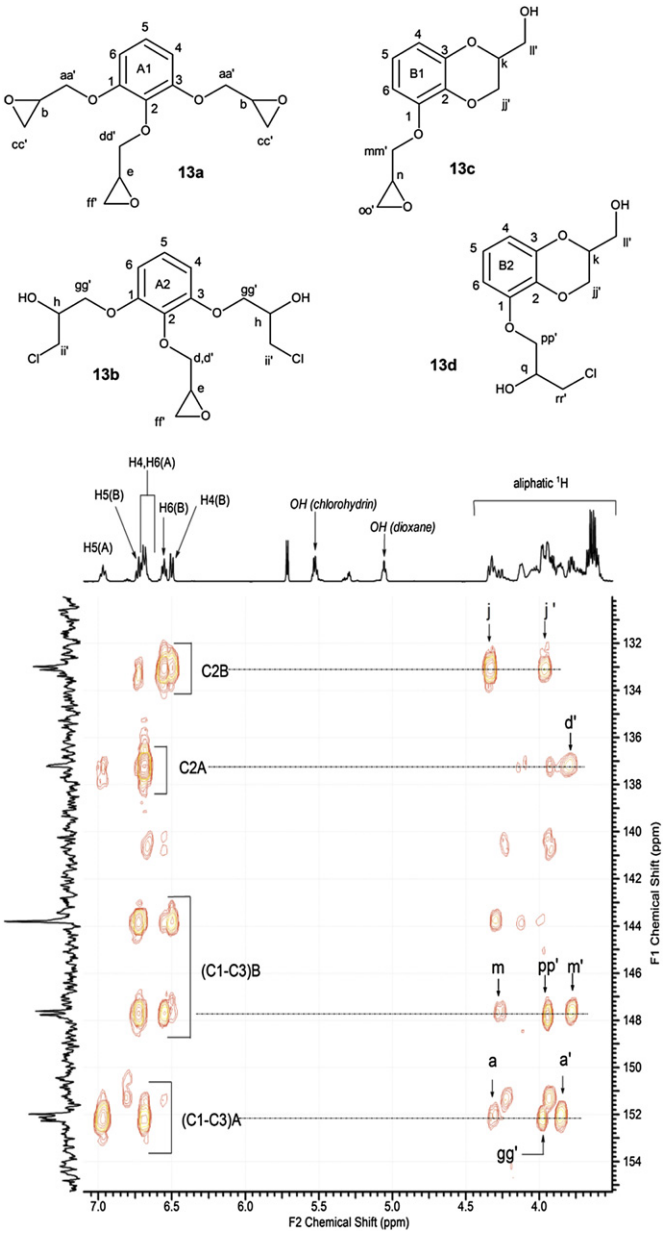


Fig. 2. HMBC spectrum of compounds **13a** and **13d** in DMSO-d_6 showing correlations between methylene protons of the substituent groups and quaternary carbons of the aromatic rings.

The predominance of mechanism B was also observed by Pchelka et al.[43] during the synthesis of 3-aryloxy-1,2-epoxypropanes. Indeed, 1-chloro-3-aryloxypropan-2-ols **17** were mainly obtained when the phenol substituents were electron withdrawing groups.

On the other hand, the study of the O-glycidylation mechanism of these different phenolic compounds allowed us to determine the origin of the formation of benzodioxane derivative. Indeed, the oxirane ring introduced via mechanism A in the first substitution step (in the case of 4-methylcatechol **1** and pyrogallol **7**) undergoes an intramolecular nucleophilic attack from the adjacent phenolate anion to yield this cyclic by-product. In contrast, the glycidylation of gallic acid exclusively implies the mechanism B, thus preventing the production of benzodioxane derivatives despite the presence of *ortho* phenolic hydroxyls.

Finally, alcoholate **16** formed during the first step of O-glycidylation underwent the NaOH assisted intramolecular cyclization to give glycidylated derivatives.

3. Conclusions

In our ongoing research program, the feasibility to substitute bisphenol A by natural phenolic compounds in the synthesis of epoxy resins pre-polymers is studied. The results of the present work show the versatility of two phenolic compounds, 4-methylcatechol and gallic acid, to react with epichlorohydrin. The mechanism of O-glycidylation of several model phenolic compounds was investigated enabling us to establish a relationship between the chemical structures of phenolic compounds and their behaviour towards epichlorohydrin. An understanding at molecular-level of the reactivity of phenolic monomers towards glycidylation constitutes an essential step in the development of bio-based epoxy resins using tannin polymers as phenolic sources.

4. Experimental section

4.1. General

Gallic acid (97.5%), 4-methylcatechol (≥95.0%), resorcinol (≥99.0%), protocatechuic acid (≥97.0%), pyrogallol (≥99.0%), epichlorohydrin (99.0%), $BnEt_3NCl$ (≥98.0%) and sodium hydroxide (≥98.0%) were purchased from Sigma–Aldrich France.

All the reactions were monitored by TLC performed on silica gel 60 F_{254}. NMR spectra were acquired on VARIAN Unity-Inova 500 MHz spectrometer (Varian NMR instruments, Palo Alto, CA), operating at 500.05 MHz for ^1H and 125.75 MHz for ^{13}C, using a 5 mm indirect detection *Z*-gradient probe. All samples were dissolved in DMSO-d_6. The chemical shifts were reported to that of internal DMSO-d_6, at 2.5 ppm for ^1H and 39.5 ppm for ^{13}C. Assignments of both proton and carbon resonances, identification and structure characterization of products were performed using several of NMR experiments: Homonuclear ^1H 1D and 2D (DOSY, COESY, ROESY and 1D selective TOCSY) and heteronuclear $^1H-^{13}C$ 2D (HSQC and HMBC) experiments. Spectra were processed and analysed using either VNMRJ or ACD/Labs software. ESI-MS analyses in positive mode were performed using a Brucker Daltonics Ion trap mass spectrophotometer (Bremen, Germany) coupled to Reversed-Phase Ultra Performance Liquid Chromatography (UPLC). Samples (5 μL) were directly injected to the UPLC system coupled to ESI-MS. The liquid chromatography system was an Acquity UPLC (Waters, Milford, MA) equipped with a Photodiode Array Detector. The column was a BEH C8 1.0×50 mm, 1.7 μm. The flow rate was 0.30 mL min^{-1} and the gradient conditions were solvent A (H_2O); solvent B (CH_3CN); initial 0.1% B; 0–3 min, 30% B linear; 3–6 min, 60% B linear; 6–8 min, 99.9% B linear.

4.2. General procedure for the glycidylation of phenolic compounds

A 100 mL two-necked flask equipped with a condenser, a septum cap and magnetic stirring bar was charged with 5 mmol of phenolic compound in epichlorohydrin (4 M equiv/OH), the suspension was heated at 100 °C and benzyltriethylammonium chloride (0.05 M equiv/substrate) was added. After 1 h, the solution was cooled to 30 °C and the aqueous solution of NaOH 20 wt % (2 M equiv/OH) with 0.05 M equiv of phase transfer catalyst ($BnEt_3NCl$) were added. The mixture was stirred vigorously for 90 min. Water (30 mL) was added to the reaction mixture and the aqueous phase was extracted with 3×30 mL of ethyl acetate. The organic phase was washed with 40 mL of brine then dried over $MgSO_4$ and vacuum concentrated. Crude products were purified by silica gel chromatography using petroleum ether/ethyl acetate (PE/EA) system.

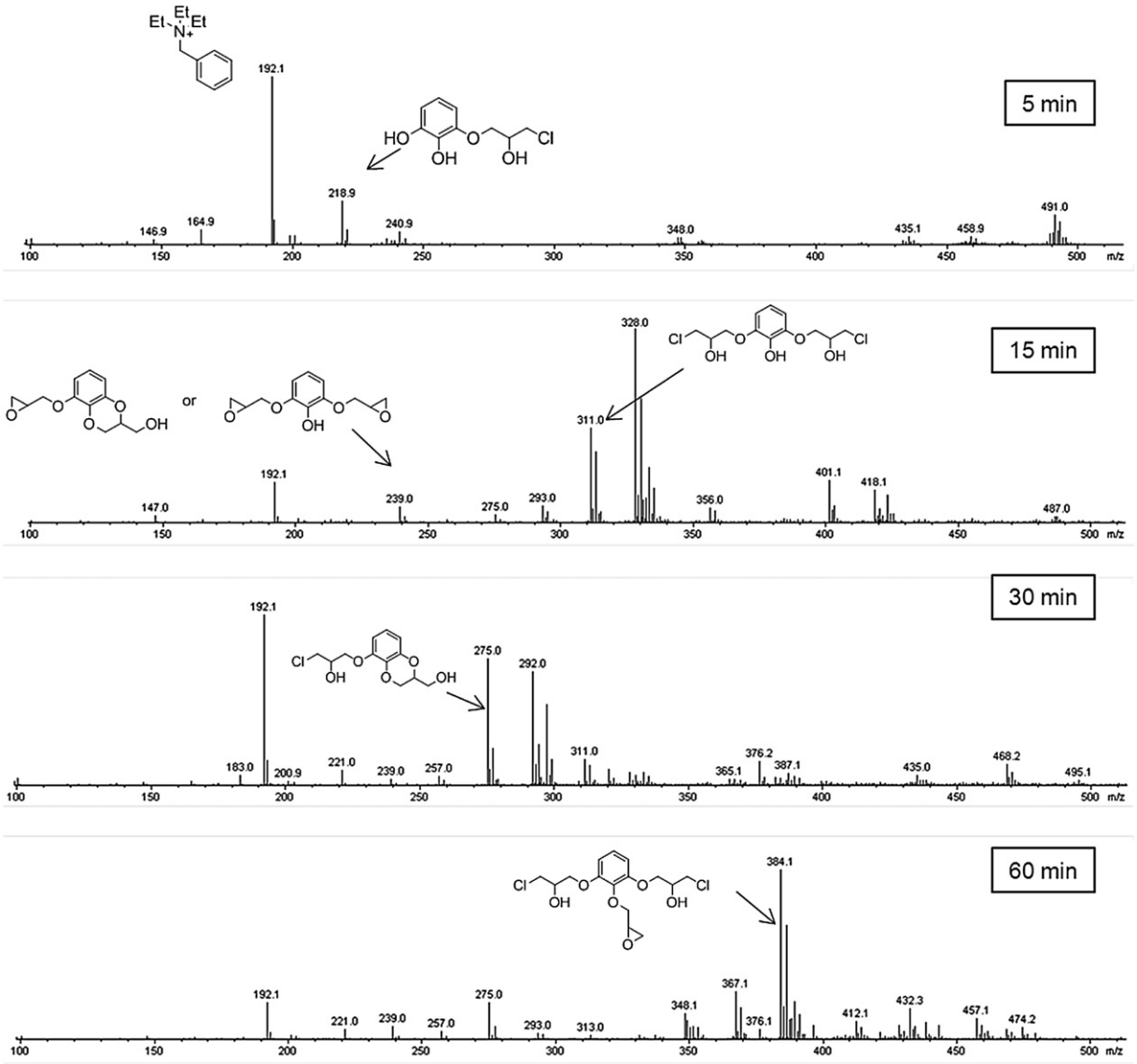
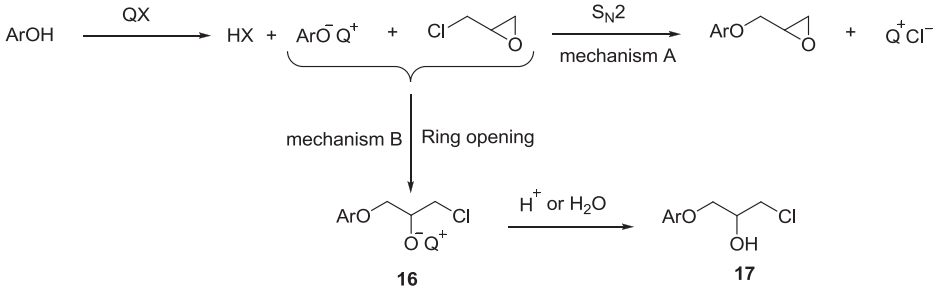


Fig. 3. Positive mode ESI-MS mass spectra of pyrogallol O-glycidylation.

4.2.1. 2,2′-(4-Methyl-1,2-phenylene)bis(oxy)bis(methylene)dioxirane ***2***. PE/EA, 70:30, colourless oil, 1.7 mmol, 34% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.22 (s, 3H, Me), 2.69 (m, 2H, a′,d′), 2.83 (m, 2H, a,d), 3.32 (m, 2H, b,c), 3.78 (m, 1H, f′), 3.81 (m, 1 H, c′), 4.25 (dd, J=11.5, 2.7 Hz, 1H, f), 4.29 (dd, J=11.4, 2.5 Hz, 1H, c), 6.69 (dd, J=8.1, 1.2 Hz, 1H, H5), 6.82 (d, J=1.2 Hz, 1H, H3), 6.87 (d, J=8.1 Hz, 1H, H6) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ=20.31 (Me), 43.5 (2C, a,d), 49.62 (2C, b,e), 69.7 (2C, c,f), 114.1 (C6), 114.82 (C3), 121.22 (C5), 130.34 (C4), 145.57 (C1), 147.61 (C2) ppm. HRMS calcd for $C_{13}H_{17}O_4$ $[M+H]^+$: 237.1127, found 237.1119.

4.2.2. (6-Methyl-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methanols ***3A*** *and* ***3B***. PE/EA, 70:30, colourless oil, 1.66 mmol, 33% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.17 (s, 3H, Me), 3.59 (m, 2H, c), 3.94 (ddd, J=11.3, 7.4, 1.9 Hz, 1H, a′), 4.08 (ddd, J=7.4, 6.4, 1.9 Hz, 1H, b), 4.26 (m, 1H, a), 5.02 (t, J=5.7 Hz, 1H, OH), 6.60 (m, 1H, H5), 6.65 (d,



Scheme 5. Mechanisms of phenolic compounds O-glycidylation.

J=2.4 Hz, 1H, H3), 6.72 (dd, J=8.1, 2.4 Hz, 1H, H6) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ=20.38, 20.41 (Me), 60.01, 60.06 (c), 65.18, 65.32 (b), 73.66, 73.75 (a), 116.64, 116.80 (C6), 117.28, 117.44 (C3), 121.59, 121.91 (C5), 130.17, 130.51 (C4), 140.9, 140.97 (C1), 142.79, 142.87 (C2) ppm. HRMS calcd for $C_{10}H_{13}O_3$ $[M+H]^+$: 181.0865, found 181.0857.

4.2.3. 3,4,5-Triglycidylether glycidyl benzoate ***5***. PE/EA, 40:60–30:70, colourless oil, 3.4 mmol, 68% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.62–2.86 (m, 8H, aa′,dd′,gg′), 3.29–3.38 (m, 4H, b,e,h), 3.90–3.94 (m, 3H, f′,i′), 4.08 (dd, J=12.4, 6.3 Hz, 1H, c′), 4.26 (qd, J=11.7, 2.9 Hz, 1H, i), 4.44 (dd, J=11.3, 2.1 Hz, 2H, f), 4.63 (dd, J=12.4, 2.5 Hz, 1H, c), 7.30 (s, 2H, H2,H6) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ=43.4 (a), 43.6 (2C, d), 43.8 (g), 49.0 (b), 49.7 (2C, e), 50.1 (h), 65.5 (c), 70.1 (2C, f), 74.0 (i), 108.4 (2C, C2, C6), 124.6 (C1), 141.6 (C4), 151.8 (2C, C3,C5), 164.0 (COO) ppm. HRMS calcd for $C_{19}H_{23}O_9$ $[M+H]^+$: 395.1342, found 395.1341.

4.2.4. Oxiran-2-ylmethyl 3,4-bis(oxiran-2-ylmethoxy)benzoate ***8***. PE/EA, 40:60, colourless oil, 3 mmol, 60% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.72–2.87 (m, 6H, aa′,dd′,gg′), 3.32–3.40 (m, 3H, b,e,h), 3.88 (dd, J=11.3, 6.6 Hz, 1H, f′), 3.94 (dd, J=11.4, 6.5 Hz, 1H, c′), 4.05 (dd, J=12.4, 6.4 Hz, 1H, i′), 4.42 (m, 2H, c,f), 4.60 (dd, J=12.3, 2.4 Hz, 1H, i), 7.12 (d, J=8.5 Hz, 1H, H5), 7.51 (d, J=1.8 Hz, 1H, H2), 7.61 (dd, J=8.5, 1.8 Hz, 1H, H6) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ=43.6–43.8 (3C, a,d,g), 49.0 (h), 49.5–49.7 (2C, b,e), 65.2 (i), 69.7–70.0 (2C, c,f), 112.7 (C5), 114.0 (C2), 121.9 (C1), 123.7 (C6), 147.5 (C3), 152.3 (C4), 165.0 (COO) ppm. HRMS calcd for $C_{16}H_{19}O_7$ $[M+H]^+$: 323.1131, found 323.1141.

4.2.5. Oxiran-2-ylmethyl 3-(hydroxymethyl)-2,3-dihydrobenzo[b][1,4] dioxine-6-carboxylate ***9***. PE/EA, 40:60, colourless oil, 0.45 mmol, 9% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.71 (dd, J=5.0, 2.6 Hz, 1H, a′), 2.83 (t, J=4.6 Hz, 1H, a), 3.31 (m, 1H, b), 3.64 (td, J=11.0, 5.4 Hz, 2H, dd′), 4.05 (dd, J=12.3, 6.3 Hz, 1H, c′), 4.10 (dd, J=11.0, 4.7 Hz, 1H, f′), 4.20 (m, 1H, e), 4.41 (dd, J=11.5, 2.2 Hz, 1H, f), 4.58 (dd, J=12.3, 2.6 Hz, 1H, c), 5.10 (t, J=5.5 Hz, 1H, OH), 6.99 (d, J=8.6 Hz, 1H, H5), 7.43 (d, J=1.9 Hz 1H, H2), 7.48 (dd, J=8.6, 1.9 HZ, 1H, H6) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ=43.82 (a), 49.05 (b), 59.69 (d), 65.13 (c) 65.51 (f), 73.59 (e), 117.12 (C5), 118.06 (C2), 122.40 (C1), 122.82 (C6), 142.88 (C3), 147.57 (C4), 164.82 (C00) ppm. HRMS calcd for $C_{13}H_{15}O_6$ $[M+H]^+$: 267.0869, found 267.0861.

4.2.6. 2,2′,2″-(Benzene-1,2,3-triyltris(oxy))tris(methylene)trioxirane ***10***. PE/EA, 40:60, colourless oil, 33% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.59–2.83 (m, 6H, aa′, dd′), 3.29–350 (m, 3H, b,e), 3.82 (m, 1H, f′), 3.87 (m, 2 H, c′), 4.12 (m, 1H, f), 4.32 (m, 2H, c), 6.69 (d, J=8.4 Hz, 2H, H4 and H6), 6.74 (t, J=8.4 Hz, 1H, H5) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ=43.65 (2C, a), 43.50 (1C, d), 49.78 (2C, b), 50.26 (1C, e), 69.75 (2C, c), 73.95 (1C, f), 107.43 (2C, C4 and C6), 123.75 (C5), 137.31 (C2), 152.39 (2C, C1 and C3) ppm. HRMS calcd for $C_{15}H_{19}O_6$ $[M+H]^+$: 295.1123, found 295.1136.

4.2.7. (5-(Oxiran-2-ylmethoxy)-2,3-dihydrobenzo[b][1,4]dioxin-2-yl) methanol ***11***. PE/EA, 40:60, colourless oil, 33% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.68–2.83 (m, 2H, gg′), 3.31 (m, 1H, h), 3.62 (m, 2H, jj′), 3.78 (dd, J=11.3, 6.6 Hz, 1H, i′), 3.96 (dd, J=11.2, 2.1 Hz, 1H, l′), 4.10 (dd, J=5.7, 2.8 Hz, 1H, k), 4.26 (dd, J=11.3, 2.6 Hz, 1H, i), 4.33 (m, 1H, l), 5.05 (t, J=5.6 Hz, 1H, OH), 6.50 (dd, J=8.3, 1 Hz, 1H, H4′), 6.54 (dd, J=8.3, 1 Hz, 1H, H6′), 6.94 (t, J=8.3 Hz, 1H, H5′) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ=43.78 (1C, g), 49.70 (1C, h), 59.83 (1C, j), 64.86 (1C, l), 69.94 (1C, i), 73.52 (1C, k), 105.73 (C6′), 109.94 (C4′), 120.06 (C5′), 132.98 (C2′), 143.97 (C3′), 147.82 (C1′) ppm. HRMS calcd for $C_{12}H_{15}O_5$ $[M+H]^+$: 239.0919, found 239.0912.

4.3. Reactions of phenolic compounds with epichlorohydrin in the presence of benzyltriethylammonium chloride

A mixture of phenolic compounds (10 mmol), epichlorohydrin (4 M equiv/OH) and benzyltriethylammonium chloride (0.05 M equiv/substrate) was stirred at 100 °C for 1 h in a 100 mL flask equipped with a reflux condenser. The reaction mixture was cooled to room temperature and thereto was added 40 mL of hexane to remove the excess of epichlorohydrin. This operation was repeated twice. The crude product was then filtrated over silica using ethyl acetate to yield the following products:

4.3.1. Mixture of 3-chloro-2-hydroxypropyl 4-(3-chloro-2-hydroxypropoxy)-3,5-dihydroxybenzoate ***12a*** *(32% yield), 3-chloro-2-hydroxypropyl 3,4-bis(3-chloro-2-hydroxypropoxy)-5-hydroxybenzoate* ***12b*** *(23% yield) and 3-chloro-2-hydroxypropyl 3,4,5-tris(3-chloro-2-hydroxypropoxy)benzoate* ***12c*** *(15% yield).* Brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.75 (m, 18H, cc′,kk′,ff′), 4.01 (m, 23H, aa′,gg′,dd′,e,h and b), 4.23 (m, 4H, aa′), 5.59 (m, 7H, OH), 7.01 (s, 1H, H_{Ar}(A)), 7.10 (d, J=1.8 Hz, 1H, H6(B)), 7.20 (d, J=1.9 Hz, 1H, H2(B)), 7.31 (s, 1H, H_{Ar}(C)), 9.51 (s, 2H, OH(A)), 9.64 (s, 1H, OH(B)) ppm.

4.3.2. Mixture of ***13a–13d***. Brown oil, 77% total yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.59 (m, f′), 2.68 (m, o′), 2.72 (m, c′), 2.74–2.76 (m, f), 2.82–2.83 (m, o), 2.83–2.84 (m, c), 3.28 (m, e), 3.31 (m, n), 3.33 (m, b), 3.59–3.64 (m, ll′), 3.65–3.77 (m, ii′ and rr′), 3.78–3.80 (m, m′), 3.79–3.83 (m, d′), 3.85–3.87 (m, a′), 3.93–3.94 (m, pp′), 3.95–3.97 (m, j′), 3.97–3.98 (m, gg′), 4.01–4.05 (m, h and q), 4.10–4.13 (m, d), 4.12 (m, k), 4.24–4.27 (m, m), 4.30–4.33 (m, a), 4.32–4.34 (m, j), 5.04 (m, OH dioxane), 5.51 (m, OH chlorohydrin), 6.49–6.51 (m, $H4_B$), 6.54–6.57 (m, $H6_B$), 6.68–6.71 (m, $(H4\text{-}H6)_A$), 6.72–6.74 (m, $H5_B$), 6.95–6.99 (m, $H5_A$). ^{13}C NMR (125 MHz, DMSO-d_6) δ=43.67–43.78 (c,f,o), 46.81 (i,r), 49.74 (b,e,n), 59.83 (l), 64.86 (j), 68.63 (h,q), 69.15–69.89 (a,d,g,m,p), 73.46 (k), 105.72–105.92 (C6 B), 107.12–107.43 ((C4–C6) A), 109.96 ($C4_B$), 120.06 ($C5_B$), 123.74 ($C5_A$), 133.98–132.12 (C2 B), 137.22 (C2 A), 147.77–143.8 ((C1–C3) B), 151.9–152.27 ((C1–C3) A) ppm.

4.3.3. 1-Chloro-3-(3-(oxiran-2-ylmethoxy)phenoxy)propan-2-ol ***15***. Brown oil, 8.1 mmol, 81% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ=2.69 (m, 1H, c′), 2.83 (m, 1H, c), 3.31 (dd, J=6.6, 3.3 Hz, 1H, b), 3.66 (dd, J=11.1, 5.4 Hz, 1H, f′), 3.74 (dd, J=11.1, 4.6 Hz, 1H, f), 3.80 (dd, J=11.4, 6.6 Hz, 1H, a′), 3.96 (m, 2H, d,d′), 4.02 (dd, J=10.3, 5.1 Hz, 1H, e), 4.30 (d, J=11.4 Hz, 1H, a), 5.54 (d, J=5.2 Hz, 1H, OH), 6.54–6.56 (m, 3H, H2, H4 and H6), 7.18 (t, J=8.4 Hz, 1H, H5) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ=43.4 (c), 46.4 (f), 49.3 (b), 66.59 (e), 68.96 (2C, c and d), 101.27 (C2), 106.8 (2C, C6 and C4), 130.02 (C5), 159.41 (C1), 159.57 (C3) ppm. HRMS calcd for $C_{12}H_{16}ClO_4$ $[M+H]^+$: 259.0737, found 259.0735.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.079.

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