Synthesis of branched cores by poly-*O*-alkylation reaction under phase transfer conditions. A systematic study

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HIGHLIGHTS

- ► The formation of branched cores from polyols was systematically studied.
- ► Effects of concentration and sequence of addition of reactants were systematically evaluated.
- ► The obtained compounds were characterized by FT-IR, ^{1}H and ^{13}C NMR.

GRAPHICAL ABSTRACT
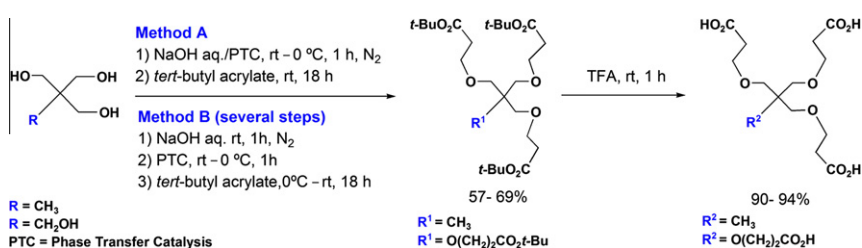
ABSTRACT

In the present paper is described a systematic study of poly-*O*-alkylation reactions of pentaerythritol (PE) and 1,1,1-*tris*(hydroxymethyl)ethane (TME) by 1,4 Michael addition, under phase transfer catalysis (PTC), considering the effect of: (1) the organophilicity of PTC (three different catalysts were tested), (2) PTC concentration (from catalytic to equimolar conditions), and (3) the regime of addition of reactants coexisting in the aqueous phase of the heterogeneous reaction system. The less organophilic transfer agent showed the best performance on these reactions. In our case, benzyltriethylammonium chloride (TEBAC) gathers the best features. The presence of NaOH as base, promotes the interfacial mechanism and not the bulk one. Out of the optimal range of concentration of NaOH (35–40%), competition between nucleophiles can occur, due to the saturation of the medium. Regarding the regime of addition of reactants, the scenario where NaOH and TEBAC are less time in contact, favors the formation of the desired products. Finally, the deprotection of *tert*-butyl groups of the poly-*O*-alkylated compounds is described, to get branched cores with terminal carboxylic acid groups in good yields (90–94%). Spectroscopic properties, such as IR, ^{1}H and ^{13}C NMR, of the synthesized compounds are also described.

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1. Introduction

Phase transfer catalysis (PTC) to carry out chemical reactions in heterogeneous media, is a very important and practical methodology extensively used by industry and academia. Detailed description of concepts and mechanistic features can be found in numerous review papers [1–6]. In organic synthesis, reactions like alkylation of phenols [7], addition reactions on conjugate compounds [8], alkylation of phosphine boranes [9] and asymmetric syntheses [10], among others, have been carried out under this methodology [11,12] with a remarkable improvement in yields.

The alkylation of aliphatic alcohols to form ether linkages is a key reaction when macromolecules (polymers and dendrimers) with hydrophilic features are synthesized [13–15].

Of particular interest in our group has been the synthesis of dendrimers [16,17] and hyperbranched polymers [18] soluble in aqueous media, and recently we focused on tetra- and trifunctional hypercores such as pentaerythritol (PE) and 1,1,1-*tris*(hydroxymethyl)ethane (TME), to construct highly polar dendrimers. The poly-*O*-alkylation of PE and TME by 1,4-addition reactions toward *tert*-butyl acrylate, under PTC conditions, is used to obtain the expected products shown in Fig. 1. The subsequent hydrolysis of the *tert*-butyl groups from **2** and **9** give rise to terminal carboxylic acids for further coupling reactions with preformed dendrons, in a convergent fashion [19].

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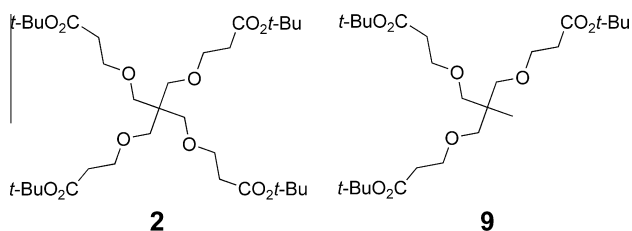
Fig. 1. Hypercores to construct dendritic scaffolds for bioapplications. (**2**): PE tetraalkylated and (**9**) TME trialkylated.

The poly-*O*-alkylation reactions of polyols by Williamson etherification assisted by catalytic amounts of quaternary ammonium salts have been reported previously [20–23].

In the present paper is reported a systematic study on the performance of the poly-*O*-alkylation of pentaerythritol (PE) and 1,1,1-*tris*(hydroxymethyl)ethane (TME) by 1,4 Michael addition, under PTC conditions, considering the effect of: (1) the organophilicity of PTC (three different catalysts were tested: benzyltriethylammonium chloride (TEBAC), tetrabutylammonium bromide (TBAB) and benzylhexadecyldimethylammonium chloride (HDBAC), (2) PTC concentration (from catalytic to equimolar conditions) and (3) the regime of addition of reactants coexisting in the aqueous phase of the heterogeneous reaction system. The variation of parameters above mentioned, strongly impact the selectivity and yield of the alkylation process.

2. Results and discussion

The polyols PE (**1**) and TME (**8**) were successfully poly-*O*-alkylated by 1,4 Michael addition reaction in presence of *tert*-butyl acrylate, under PTC conditions, followed by deprotection of compounds **2**, **5**, **9** to obtain the hypercores. The general scheme of reactions is shown in Fig. 2.

All the products were purified and verified by spectroscopic methods (FT-IR, NMR, GC–MS). Of particular interest are molecules **6** and **12** with terminal –COOH groups, since they are intended to be used as hypercores of dendrimers with potential application in drug carrying. The hydrolysis reaction of compounds **2** or **9** in presence of trifluoroacetic acid (TFA) is highly efficient (90–94% yield).

In order to optimize the synthetic route, several parameters involved in phase transfer protocols were systematically modified, as will be discussed below.

2.1. Effect of PTC organophilicity

The effect of the organophilicity of the PTC on the yields of polyalkylation of PE and TME was evaluated by the use of three different quaternary ammonium salts; TEBAC, TBAB and HDBAC, whose affinity for the organic phase increases in the following order: TEBAC < TBAB < BHDAC [24]. The results are shown in Table 1. Standarized conditions earlier reported by Dupraz et al. [25] were used in order to contrast only the chemical nature of PTC.

From Table 1, the poly-*O*-alkylation in presence of HDBAC (the most organophilic PTC), does not occur, independently of the polyol. A similar behavior was reported before [26]. Eventhough the reactivity of the PTC is directly related to the accessibility toward the central cation, it has been documented that the degree of organophilicity becomes more critical than the steric hindrance, especially when the interfacial mechanism is involved (see Ref. [1]). Thus, the low solubility of HDBAC in aqueous medium do not favor the 1,4-addition reaction to form the *O*-alkylated product. The ammonium salt; TEBAC with the lowest organophillicity, provided the best results in terms of yield for both polyols. In the classical interfacial mechanism proposed by Makosza, the hydroxide ion

deprotonates a molecule of organic substrate located near the aqueous–organic interface. In the case of reaction depicted in Fig. 2, the deprotonation occurs in the aqueous phase, and the formed nucleophile is drawn to the organic phase, assisted by the PTC. Thus, as TEBAC is the most hydrophilic, remains in the aqueous phase until the "load" of nucleophile is enough to migrate to the interface, where nucleophilic addition reaction takes place. The species TEBAC$^+$ *tert*-butyl acrylate$^-$ at the interface is formed primarily by the high probability of mutual collisions between TEBAC$^+$OH$^-$ and *tert*-butyl acrylate, since TEBAC has adequate organophilicity, and its diffusion rate from the bulk to a "fresh" interface is sufficiently fast, due to its moderate molecular size [27]. On the other hand, to rationalize the small but clear difference in performance between TEBAC and TBAB, a simplistic model of anion exchange on the PTC was simulated in a continuum aqueous medium (dielectric constant; ε = 81), by applying the density functional theory (DFT), and Gibbs free energies were obtained by frequency calculations of the previously optimized geometries (see Supporting information).

In order to form an ion pair with either PE or TME, and migrate to organic phase, the dissociation of PTCs should take place easily in water. The ease of dissociation of PTCs was evaluated by an ion exchange reaction with NaOH$_{aq}$. Fig. 3 shows the ΔG values, calculated at DFT level of theory, where it is observed that, in case of TEBAC is slightly more favorable this exchange ($\sim$2 kcal), which might be related to the increased electrostatic availability of the positive charge of central nitrogen atom of TEBAC, due to its shorter aliphatic chains. Obviously in aqueous media, all the ions will be dissociated; however, these calculations give an indication of the disposition of the PTC to interact with another counteranion. Hence, TEBAC was the PTC used in further reactions.

2.2. Effect of base concentration

In standard conditions of *O*-alkylation reactions mediated by PTC is suggested a concentration of 40% (w/w) of NaOH. A quick examination of the NaOH concentration effect on the reaction yields showed that a concentration between 35% and 40% effectively provides the best performance (see Table 2).

It is expected that, by increasing the concentration of base (NaOH), the water present is unable to hydrate all ions. Consequently, the basicity increases so as to compete like nucleophile with the organic substrate at the interface; resulting in byproducts (Hofmann degradation for instance), others than the poly-*O*-alkylation products.

2.3. Effect of PTC concentration

The concentration of PTC (from equimolar to catalytic amounts) proved to be a parameter that significantly impacts the performance of the reaction. The results of this evaluation are shown in Table 3 for the polyol PE. A gradual decrease in the concentration of PTC leads to better performance of the *O*-alkylation reaction.

At low concentrations of PTC is feasible to assume that a stepwise transfer of nucleophilic groups to the interface, assisted by the PTC, can occurs. As the poly-*O*-alkylation reaction proceeds for one nucleophile at a time, a suitable hydrophobic balance is achieved to drag the system to the interface and eventually into the organic phase, thus completing successfully the reaction.

When the PTC concentration increases, a rapid saturation of the interface with poly-*O*-PTC species can takes place, with an inadequate balance to reach the reaction site. Results from Table 3 again point out to an interfacial mechanism, frequently suggested for phase transfer reactions involving PTC/OH systems.
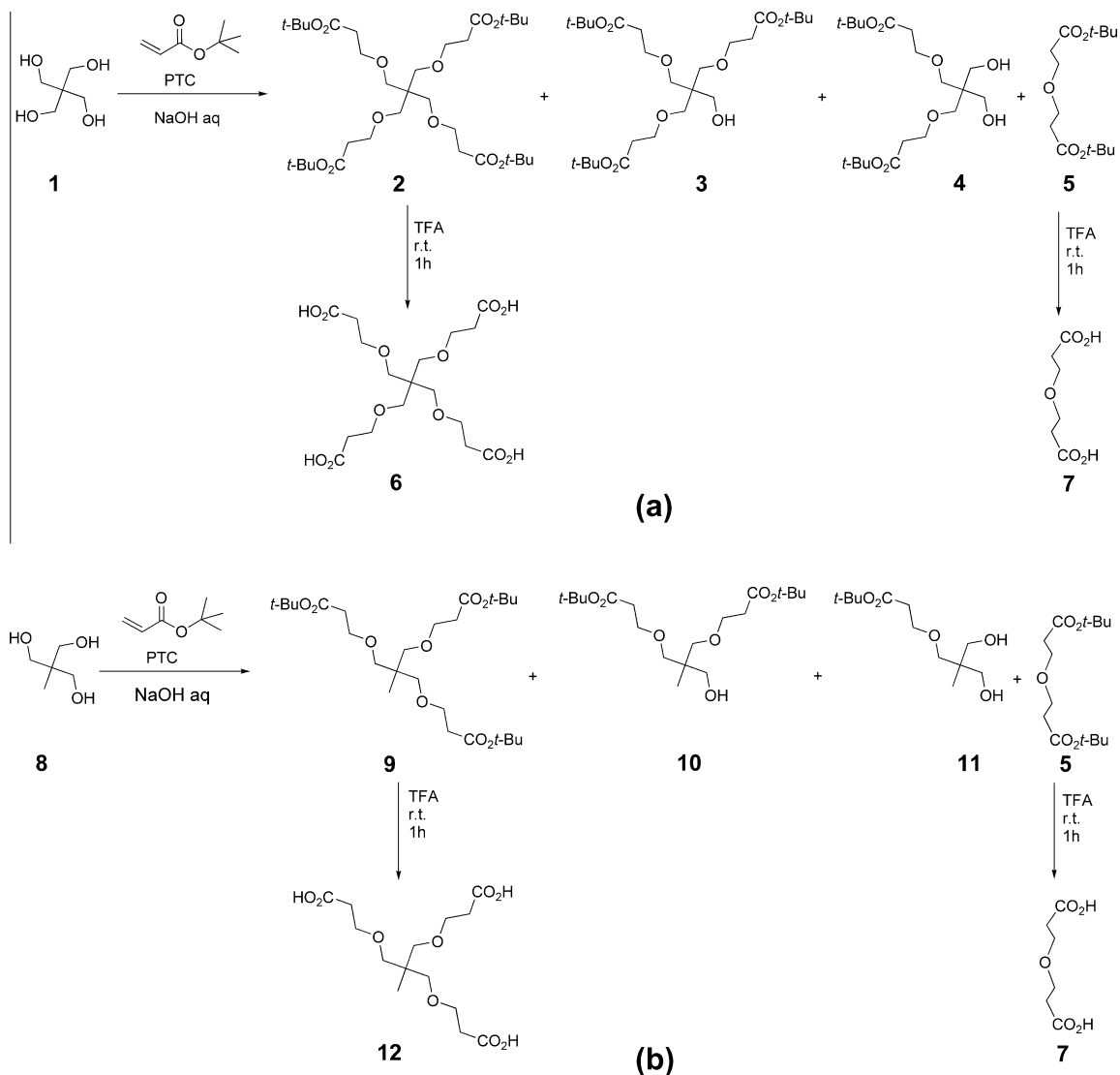
Fig. 2. General scheme of O-alkylation of polyols for: (a) PE (**1**) and (b) TME (**8**).

Table 1
Effect of organophilicity of PTC on the polyalkylation yields.

Polyol	Yield (%) of poly-O-alkylation		
	HDBAC	TBAB	TEBAC
PE[a]	–	37.3	41.1
TME[b]	–	39.5	45.1

[a] Experimental conditions: 1.0 mmol PE, 4.1 eq. tert-butyl acrylate, 1.0 mmol PTC, 1.0 mL of aqueous NaOH (40%), 24 h, r.t.
[b] Experimental conditions: 1.0 mmol TME, 3.1 eq. tert-butyl acrylate, 1.0 mmol PTC, 1.0 mL of aqueous NaOH (40%), 24 h, r.t.

2.4. Effect of regime of addition

Two regimes of addition of reactants were tested in order to study the effects on the performance and selectivity of the O-alkylation of PE and TME under PTC conditions (Fig. 4). In a first case (labeled as A), a mixture of the polyol, aqueous NaOH and catalyst (TEBAC) was made in deionized water (stage 1), and subsequently the tert-butyl acrylate was added under N_2 atmosphere and ice bath temperature (stage 2). Following this order of addition, alkylation conversions of 69% and 76% were obtained for PE and TME respectively.
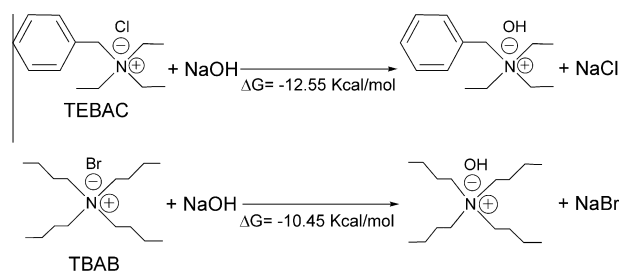

Fig. 3. Anion exchange modeled at the B3LYP/6-31+G* level to illustrate the ease of dissociation of PTCs in aqueous medium.

In the second procedure labeled as B, a first mixing stage between polyol and aqueous NaOH in deionized water took place and, after an hour an aqueous solution of catalyst was added (stage 2). Finally the tert-butyl acrylate was added under N_2 atmosphere and ice bath temperature (stage 3). In this case, the conversions were 83% and 89% for the alkylation of PE and TME respectively. From the total conversion, the selectivity of formed products is shown in Fig. 4.

Table 2
Aqueous NaOH concentration effect.

NaOH$_{aq}$ (%, w/w)	Yield[a] (%) of poly-O-alkylation	
	PE[a]	TME[b]
25	28.5	23.6
30	33.6	31.9
35	38.5	50.1
40	41.1	45.6
45	37.3	40.1
50	35.0	30.1

[a] Experimental conditions: 1.0 mmol PE, 4.1 eq. *tert*-butyl acrylate, 0.5 mmol de TEBAC, 0.8 mL of aqueous NaOH, 24 h.
[b] Experimental conditions: TME 1.0 mmol, 3.1 eq. *tert*-butyl acrylate, 0.5 mmol de TEBAC, 0.8 mL of aqueous NaOH, 24 h.

Table 3
Evaluation of the effect of PTC concentration on the O-alkylation reaction of PE.

PE/TEBAC[a]	Yield (%) of poly-O-alkylation[b]	
	NaOH$_{aq}$ (35%)	NaOH$_{aq}$ (40%)
1.0/1.20	32	36
1.0/1.00	39	41
1.0/0.75	45	45
1.0/0.50	52	50
1.0/0.20	57	55

[a] Experimental conditions: 1.0 mmol PE, 4.1 eq. *tert*-butyl acrylate, 0.8 mL of aqueous NaOH, rt, 18 h.
[b] Isolated yield of compound **2**.

In order to rationalize the minor conversion by sequence A compared with sequence B, the analysis of degradation products and byproducts of TEBAC was made. The preliminary attack of OH− on the benzyl moiety of TEBAC (scenario A) produces a complex mixture, wherein the main product was benzyldiethylamine (80%), with lesser amount of triethylamine. The anionic exchange between OH− and Cl− in TEBAC was favored in the sequence A. On the other hand, the minor time of contact between NaOH and TEBAC (scenario B) favors the formation of the desired products.

The selectivity of alkylation of PE and TME may be rationalized in terms of the solubility of the ion pairs tri(PTC-R4) or bi(PTC-R4) at the interface, as it was observed in previous work where the influence of the carbon geometry on the selectivity of alkylation in PTC conditions was discussed [21,22]. The major organophilic character of ion pair formed by the benzyltrimethyl ammonium and PE-trisubstitued seems to be an important factor to obtain a minor yield versus benzyltrimethyl ammonium and TME-disubstituted (Fig. 5).

In contrast to previous work (Ref. [22]), in the present study were actually isolated the mono- and di-substituted products

(see Supporting information), and this would be related to two different type of reactions involved to form the ether linkages (nucleophilic substitution in the previous work and Michael addition in our case). Beyond the rationalization done in earlier studies (mainly based on rates of formation of species and their transit to the organic phase), the results obtained here again point towards an interfacial mechanism that allows the coexistence of products with a broader range of polarity, such as mono- and di-alkylated products.

On the other hand, the presence of linear ether R–O–R (compound **5** in Fig. 2) is completely consistent with the addition of OH ions to *tert*-butyl acrylate into the organic phase. The newly formed alcohol is transformed into the symmetric ether. Alkoxide ions are more lipophilic than hydroxyl ions and can therefore be extracted preferentially. Finally, it was evaluated the effect of adding an organic co-solvent (CH$_2$Cl$_2$, CHCl$_3$ and toluene) to swell the organic phase (in our case, *tert*-butyl acrylate only). The result again supports the interfacial mechanism, since the thickening of the organic phase causes a performance loss (8–10% yield). By increasing the equivalents of *tert*-butyl acrylate (organic phase) was not observed an increase in selectivity towards the desired products (molecules **2** and **9** respectively), which is consistent with the analysis done before, that points out to the interfacial mechanism with a discrete organic layer.
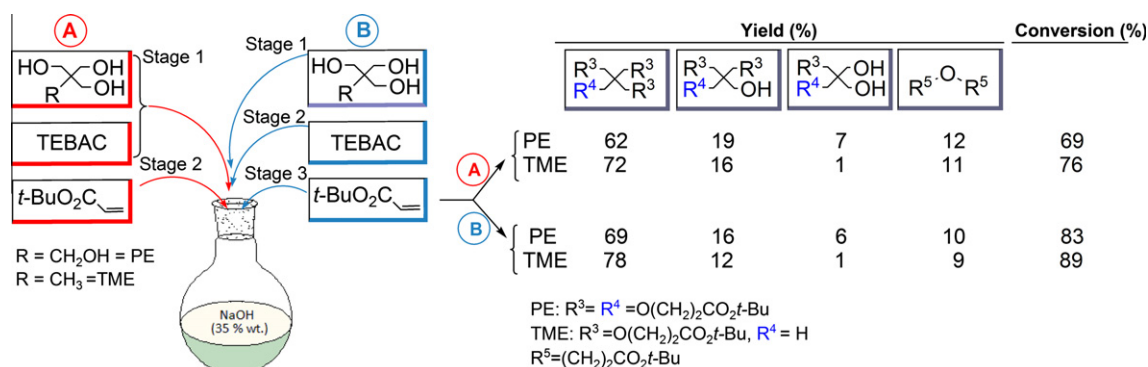
2.5. Scaling effect

Using the best conditions from previous experiments, scale-up of reactions was made by the increment in polyols amounts (Table 4). The results show that the reaction can be projected to a preparative scale, without a significant change in yields.

Fig. 6 presented below is intended to illustrate the interfacial mechanism that presumably is operating, according to all the information obtained from various experiments.

2.6. Structural characterization

To illustrate the representative bands in FT-IR, compounds **9**, **10**, **11** and **12** were chosen (see Fig. 7). Typically intense bands corresponding to carbonyl vibrations (υ(C=O), ester) appear around 1726 cm^{-1}. In case of compound **12**, the vibration of carbonyl from carboxylic acid groups is observed at 1700 cm^{-1}. Aliphatic vibrations; $\upsilon_{alif.}$(C—H), are observed from 2870 to 2974 cm^{-1}. The degree of O-alkylation for compounds **10** and **11** can be confirmed by the intensity changes of the band corresponding to υ(OH), which also is shifted from 3320 to 3399 cm^{-1} when the degree of alkylation diminishes. Compound **12** exhibits a broad band υ(COOH) from 3300 to 2872 cm^{-1}, characteristic of carboxylic acids. All compounds show the vibration υ(C—O—C) at 1100 cm^{-1}.

	R^3 ⤬ R^3 / R^4 R^3	R^3 ⤬ R^3 / R^4 OH	R^3 ⤬ OH / R^4 OH	R^{5}ˍO˸R^5	Conversion (%)
PE	62	19	7	12	69
TME	72	16	1	11	76
PE	69	16	6	10	83
TME	78	12	1	9	89

R = CH$_2$OH = PE
R = CH$_3$ = TME

PE: R^3 = R^4 = O(CH$_2$)$_2$CO$_2$*t*-Bu
TME: R^3 = O(CH$_2$)$_2$CO$_2$*t*-Bu, R^4 = H
R^5 = (CH$_2$)$_2$CO$_2$*t*-Bu

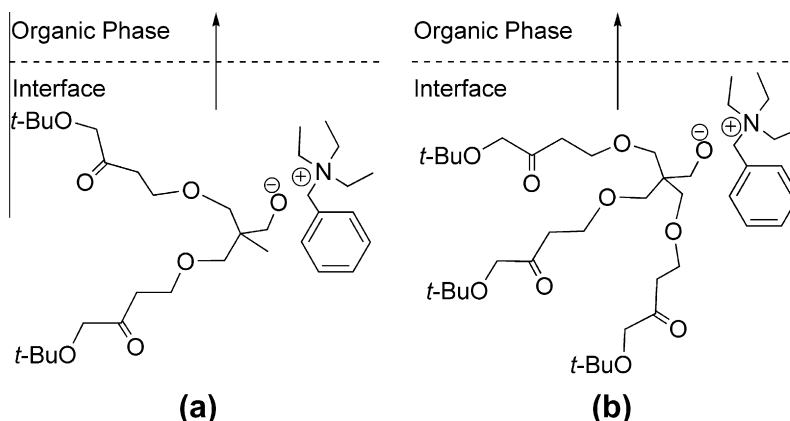**Fig. 4.** Effect of the regime of addition, path A in two stages, path B in three stages.

Fig. 5. Ion pair structures of benzyltrimethylammonium-TME-Disubstitued (a) versus benzyltrimethylammonium-*PE*-trisubstitued (b).

Table 4
Scaling of the poly-*O*-alkylation reaction of polyols by TEBAC.

Polyol (mmol)	Yield (%) of poly-*O*-alkylation	
	PE[a]	TME[b]
1	56	59
3	56	69
5	64	70
7	60	63
9	57	59

[a] Isolated yield of compound **2**.
[b] Isolated yield of compound **9**.

From the analysis of ^{1}H NMR spectra (300 MHz, CDCl$_3$) of compounds **9**, **10** and **11** (Fig. 8) is observed that, as the degree of *O*-alkylation from **9** to **11** diminish, there is a shift of methyl protons of TME towards higher fields (from 0.89 to 0.77 ppm). A similar behavior is experimented by methyl protons of *tert*-butyl groups from 1.45 to 1.42 ppm, whose signal intensity decreases with incomplete alkylation (from compound **9** to **11**), and the methylene protons of TME get shifted to lower fields, presumably due to inductive effects.

3. Conclusions

The use of quaternary ammonium salts as phase transfer agents represents an appropriate protocol to carry out poly-*O*-alkylation of highly polar polyols. The less organophilic transfer agent is the better to performance these reactions. In our case, TEBAC gathers the best features. The better performance of the less organophilic PTC and the marginal yields obtained when the organic phase was swelled with a co-solvent (CH$_2$CH$_2$, CHCl$_3$ or toluene), are evidences that support an interfacial mechanism and not the bulk one, proposed by Stark [6]. Additionally, the dependence of NaOH concentration also points out toward this scenario. It is important not to exceed the optimum concentration of NaOH (35–40%) in order to prevent saturation and competition between nucleophiles. Concerning the regime of addition of reactants, the scenario where NaOH and TEBAC are less time in contact, favors the formation of the desired products.

4. Experimental section

4.1. Materials

Tetrabutylammonium bromide (TBAB), benzyltriethylammonium chloride (TEBAC), benzylhexadecyldimethylammonium chloride (BHDAC), pentaerythritol (PE), 1,1,1-*tris*(hydroximethyl)

ethane (TME), and *tert*-butyl acrylate, trifluoroacetic acid (TFA) were purchased from Aldrich. Sodium hydroxide, diethyl ether, hexanes, ethyl acetate, dichloromethane, were purchased from Tecsiquim (Mexico). All reactants and solvents were used as received.

4.2. Analytical techniques

Mass spectroscopy (GC–MS) were performed on a Shimadzu GC-2010/MS-QP2010s system using a capillary column separation (30 m × 0.32 mmID Rtx®-5MS (RESTEK) with a 5 m integra-guard column). ^{1}H and ^{13}C NMR were obtained on a Bruker Advance 400 and Jeol Eclipse 300 MHz spectometer in CDCl$_3$, DMSO-d$_6$ or D$_2$O. FT-IR spectra were run on Nicolet 6700 FT-IR spectrometer.

4.3. Synthesis of polyether compounds. General procedure for the polyetherification of Pentaerythritol

3-[3-(2-tert-Butoxycarbonyl-ethoxy)-2,2-bis-(2-tert-butoxycarbonyl-ethoxymethyl)-propoxy]-propionic acid tert-butyl ester, **2**: Pentaerythritol (**1**, 136.15 mg, 1.0 mmol) was added to NaOH solution (0.8 mL, 40.0% w), Then it was purged and an atmosphere of N$_2$ gas was applied to the reaction mixture using rubber balloon and protected from light. The mixture was vigorously stirred at room temperature for 1 h. Then, benzyltriethylammonium chloride (TEBAC) (0.5 mmol, 0.5 eq. in 2 mL distilled water) was added via syringe. The mixing was poured into an ice bath and *tert*-butyl acrylate (4.1 mmol, 4 eq. 0.6 mL) was dropwise. After that the reaction was maintained at room temperature for 18 h. The reaction was quenched by added 1 mL of cold water and the solution was taken up in diethyl ether (3 × 25 mL). The organic layers were washed twice with saturate NaHCO$_3$ solution (2 × 25 mL) and additional brine solution (2 × 25 mL), then dried over MgSO$_4$. The solvent was removed by evaporation and the products were purified by column chromatography using a mixture of hexane and ethyl acetate as eluent to afford 363 mg (**2**, 56%) ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.46 (s, 36 H), 2.46 (t, *J* = 6.2, 8 H), 3.61 (t, *J* = 6.2, 8 H), 3.37 (s, 8 H). ^{13}C NMR (CDCl$_3$, 400 MHz) δ 28.15, 36.42, 45.40, 67.11, 69.78, 80.12, 170.83 ppm. IR (neat) *ν*: 2976, 2930, 2870, 1728, 1251, 1100, 1068 cm^{-1}. GC–MS (EI): *m/z* calcd for C$_{33}$H$_{60}$O$_{12}$ 648, found 648 [M + 1]$^+$.

3-[2,2-Bis-(2-tert-butoxycarbonyl-ethoxymethyl)-3-hydroxy-propoxy]-propionic acid tert-butyl ester, **3**. This tris-ester was obtained as byproduct of 1,4-Michael addition in the *O*-alkylation of pentaerythritol with *tert*-butyl acrylate and it was isolated (84 mg, 13%) by silica gel chromatography with hexane–ethyl acetate gradient. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.44 (s, 27 H), 2.44 (t, *J* = 6.2, 6 H),
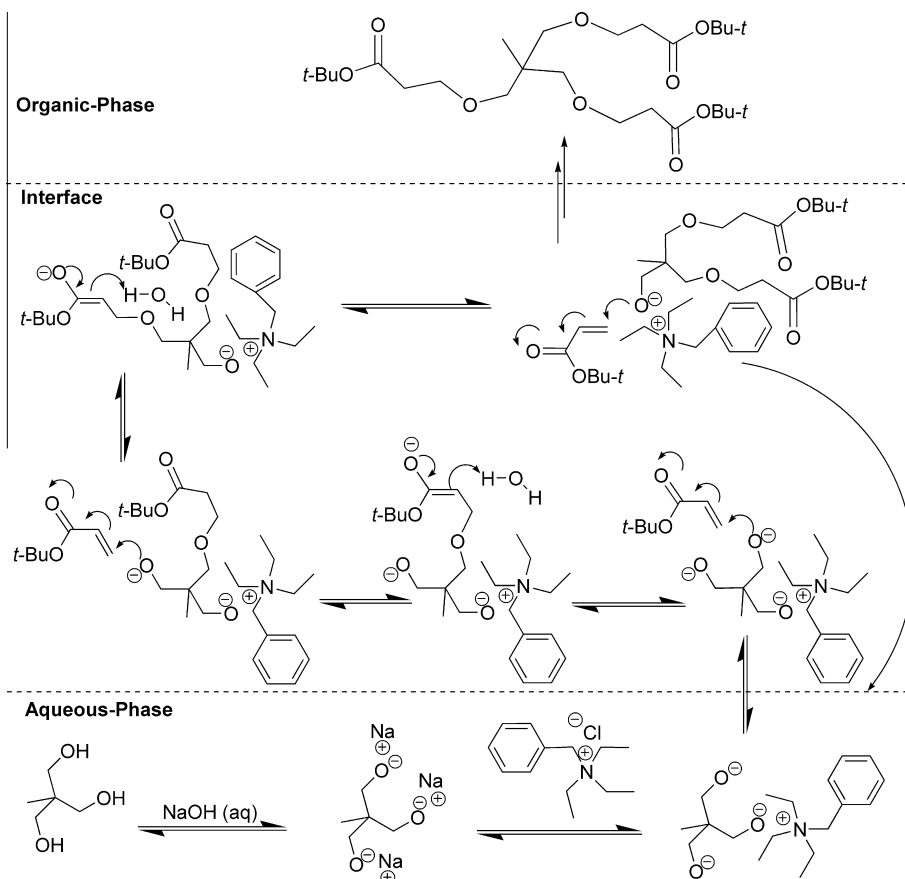
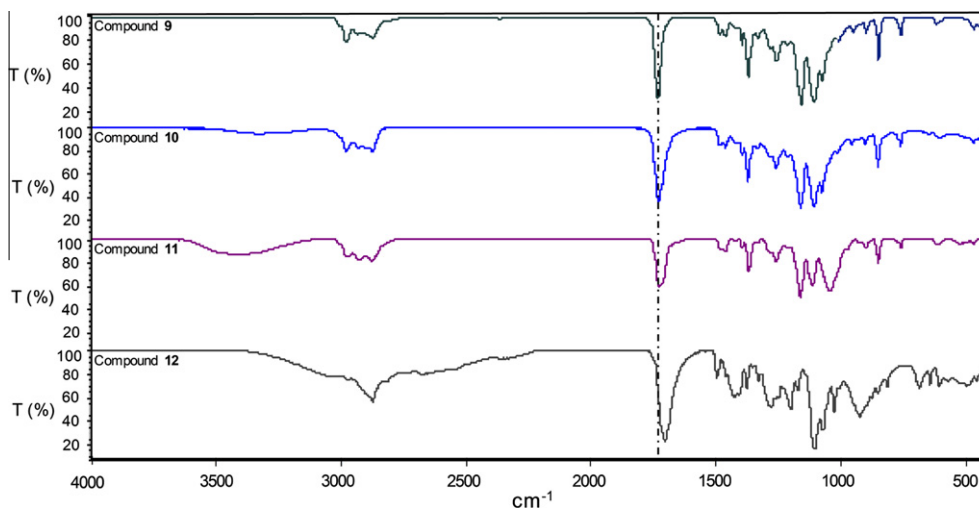**Fig. 6.** Illustration of interfacial mechanism for the poly-*O*-alkylation of PE mediated by TEBAC.

Fig. 7. Infrared spectra of compound **9**, **10**, **11**, **12**.

3.42 (s, 6 H), 3.61 (t, *J* = 6.2, 8 H), 2.38 (b, 1 H) ppm. ^{13}C NMR (CDCl$_3$, 400 MHz) δ 28.3, 36.5, 45.2, 65.6, 67.5, 71.5, 80.7, 171.1 ppm. IR *v*: 3536.2 (broad), 2976.5, 2929.8, 2870.0, 1725.5, 1253.9, 1068.1, 1102.0 cm^{-1}. GC–MS (EI): *m/z* calcd for C$_{26}$H$_{48}$O$_{10}$ 520, found 519 [M + 1]$^+$.

2,2-Bis-(2-tert-butoxycarbonyl-ethoxymethyl)-3-hydroxy-propyl-oxonium, **4**. This bis-ester was obtained as byproduct of 1,4-Michael addition in the *O*-alkylation of pentaerythritol with *tert*-butyl acrylate and it was isolated (27.45 mg, 7%) by silica gel chromatography with hexane–ethyl acetate gradient. ^{1}H NMR (CDCl$_3$,

400 MHz) δ 1.43 (s, 18 H), 2.43 (t, *J* = 6.2, 4 H), 2.58 (t, *J* = 5.9, 2 H), 3.35 (s, 4 H), 3.4 (m, 2 H), 3.58 (t, *J* = 6.4, 4 H), 3.65 (t, *J* = 5.9, 2 H) ppm. ^{13}C NMR (CDCl$_3$, 400 MHz) δ: 28.33, 35.07, 36.53, 45.44, 67.33, 70.06, 80.69, 171.50 ppm. IR (neat) *v*: 3320, 2976, 2929, 2865, 1725, 1251, 1099, 1067 cm^{-1}.

3-(2-tert-Butoxycarbonyl-ethoxy)-propionic acid tert-butyl ester, **5**. This di-ester was obtained as byproduct in the *O*-alkylation of pentaerythritol with *tert*-butyl acrylate and it was isolated (52 mg, 8%) as yelow oil by silica gel chromatography with hexane–ethyl acetate gradient. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.44 (s, 9

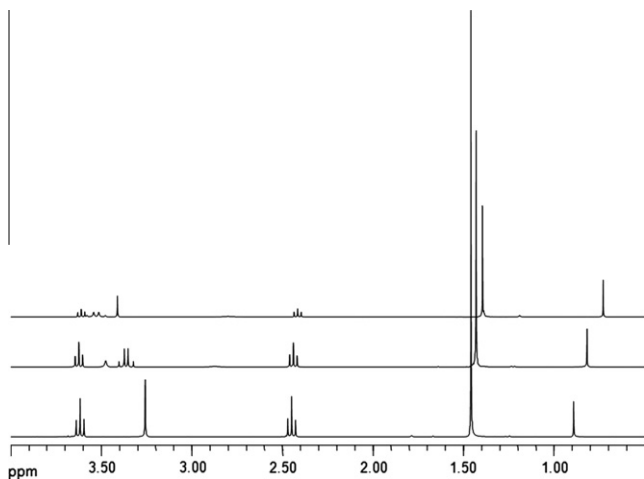H), 2.47 (t, J = 6.2, 2 H), 3.67 (t, J = 6.2, 2 H) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz) δ: 28.38, 36.63, 66.88, 80.69, 170.9 ppm. IR cm^{-1}: 2977, 2932, 2872, 1726, 1254, 1059, 1110 cm^{-1}. GC–MS (EI): m/z calcd for C$_{14}$H$_{26}$O$_5$ 274, found 274 [M + 1]$^+$.

4.4. Synthesis of poly-O-alkylation of TME

3-[3-(2-tert-Butoxycarbonyl-ethoxy)-2-(2-tert-butoxycarbonyl-ethoxymethyl)-2-methyl-propoxy]-propionic acid tert-butyl ester, **9**. The compound **9** has been prepared by following the procedure described above, TME (**8**, 120.15 mg, 1.0 mmol), NaOH solution (0.8 mL, 40.0% w). The mixture was vigorously stirred at room temperature for 1 h. Then, benzyltriethylammonium chloride (TEBAC) (0.5 mmol, 0.5 eq. in 2 mL distilled water) was added via syringe. The mixing was poured into an ice bath and *tert*-butyl acrylate (3.1 mmol, 3.0 eq. 0.45 mL) was dropwise. After work up, product **9** was obtained in 79% (353 mg) as yelow oil. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.89 (s, 3 H), 1.45 (s, 27 H), 2.44 (t, J = 6.4, 6 H), 3.24 (s, 6 H) 3.60 (t, J = 6.4, 6 H). ^{13}C NMR (CDCl$_3$, 300 MHz) δ: 17.16, 28.07, 36.39, 40.81, 67.07, 73.51, 80.23, 171.01 ppm. IR (neat) v: 2978, 2930, 2870, 1726, 1252, 1068, 1100 cm^{-1}. GC–MS (EI): m/z calcd for C$_{26}$H$_{48}$O$_9$ 504, found 504 [M + 1]$^+$.

3-[2-(2-tert-Butoxycarbonyl-ethoxymethyl)-3-hydroxy-2-methyl-propoxy]-propionic acid tert-butyl ester, **10**. Di-ester was obtained as byproduct in the *O*-alkylation of TME with *tert*-butyl acrylate and it was isolated (52 mg, 8%) as yelow oil by silica gel chromatography with hexane–ethyl acetate gradient. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.81 (s, 3 H), 1.42 (s, 18 H), 2.43 (t, J = 6.1, 4 H), 3.38 (dd, J = 11.3, J = 11.3, 4 H), 3.5 (s, 2 H) 3.64 (t, J = 6.1, 4 H) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz) δ: 17.37, 28.02, 36.20, 40.57, 67.15, 68.58, 75.2, 80.58, 171.01 ppm. IR (neat): 3320, 2976, 2929, 2870, 1726, 1252, 1110, 1068 cm^{-1}. GC–MS (EI): m/z calcd for C$_{19}$H$_{36}$O$_7$ 376, found 376 [M + 1]$^+$.

3-(3-Hydroxy-2-hydroxymethyl-2-methyl-propoxy)-propionic acid tert-butyl ester, **11**. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.77 (s, 3 H), 1.44 (s, 9 H), 2.48 (t, J = 5.8, 2 H), 3.47 (s, 2 H), 3.57 (dd, J = 15.0, J = 6.1, 4 H), 3.66 (t, J = 5.8, 2 H). ^{13}C NMR (CDCl$_3$, 300 MHz) δ: 17.19, 28.0, 35.98, 40.76, 67.1, 67.89, 75.77, 81.07, 171.46 ppm. IR (neat) v: 3399, 2974, 2923, 2873, 1724, 1254, 1108, 1068 cm^{-1}. GC–MS (EI): m/z calcd for C$_{12}$H$_{24}$O$_5$ 248, found 248 [M + 1]$^+$.

4.5. General procedure for the removal of protecting groups

3-[3-(2-Carboxy-ethoxy)-2,2-bis-(2-carboxy-ethoxymethyl)-propoxy]-propionic acid, **6**. The compound **2** (648 mg, 1 mmol) was

poured into a glass flask without degassed, after which 0.54 mL of trifluoroacetic acid (TFA, 7.0 mmol) were added. The solution was stirred at room temperature for 1 h, after which it was dissolved and washed several times in a mixture of hexane and dichloromethane, until the compound **6** was TFA free, the absence of signal from *tert*-butyl indicating complete hydrolysis was verified by ^{1}H NMR and also no signal of TFA at 164 ppm by ^{13}C NMR indicate complete deprotection and high purities obtained in good yield 94% (399 mg) of **6** as white solid, mp. 94–96 °C. ^{1}H NMR (D$_2$O, 400 MHz) δ 2.52 (t, J = 5.9, 8 H), 3.28 (s, 8 H), 3.61 (t, J = 6.0, 8 H), ^{13}C NMR (D$_2$O, 400 MHz) δ 176.4, 69.0, 66.8, 44.9, 34.4. IR (neat) v: 2870 (broad), 1726, 1252, 1068, 1100. GC–MS (EI): m/z calcd for C$_{17}$H$_{28}$O$_{12}$ 424, found 424 [M + 1]$^+$.

3-(2-Carboxy-ethoxy)-propionic acid, **7**. Desprotection of **5** (400 mg, 1.45 mmol) as above in 0.5 mL of TFA afforded 211 mg (90%) of **7** as a white solid, mp 56–58 °C. ^{1}H NMR (D$_2$O, 400 MHz) δ 2.6 (t, J = 5.9, 4 H), 3.7 (t, J = 5.8, 4 H), ^{13}C NMR (D$_2$O, 400 MHz) δ 176.0, 65.8, 34.1. IR (neat) v: 2870 (broad), 1726, 1252, 1068, 1100. GC–MS (EI): m/z calcd for C$_6$H$_{10}$O$_5$ 162, found 162 [M + 1]$^+$.

3-[3-(2-Carboxy-ethoxy)-2-(2-carboxy-ethoxymethyl)-2-methyl-propoxy]-propionic acid, **12**. Desprotection of **9** (504 mg, 1 mmol) was carried out as above in 0.5 mL of TFA afforded 302 mg (92%) of **9** as pale yellow viscous oil. ^{1}H NMR (D$_2$O, 300 MHz) δ 0.86 (s, 3 H), 2.63 (t, J = 5.9, 6 H), 3.34 (s, 6 H) 3.74 (t, J = 5.9, 6 H). ^{13}C NMR (D$_2$O, 300 MHz) δ 176.4, 73.1, 67.0 40.5, 34.5, 27.5, 16.8 ppm. IR v 2872 (broad), 1698, 1254, 1102, 1068 cm^{-1}. GC–MS (EI): m/z calcd for C$_{14}$H$_{24}$O$_9$ 336, found 336 [M + 1]$^+$.

Supplementary material

Supplementary data containing FT-IR, RMN 1H and 13C spectra, and computational details can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2013.01.034.

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