L-Arabinitol-Based Functional Polyurethanes

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ABSTRACT: Three new polymerizable diols, based on mono-, di-, and tri-*O*-allyl-L-arabinitol derivatives, were prepared from L-arabinitol as versatile materials for the preparation of tailor-made polyurethanes with varied degrees of functionalization. Their allyl functional groups can take part in thiol-ene reactions, to obtain greatly diverse materials. This "click" reaction with 2-mercaptoethanol was firstly studied on the highly hindered sugar precursor 2,3,4-tri-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol, to apply it later to macromolecules. A polyurethane with multiple pendant allyl groups was synthesized by polyaddition reaction of 2,3,4-tri-*O*-allyl-L-arabinitol with 1,6-hexamethylene diisocyanate, and then functionalized by thiol-ene reaction. The coupling reaction took place in every allyl group, as confirmed by standard techniques. The thermal stability of the novel polyurethanes was investigated by thermogravimetric analysis and differential scanning calorimetry (DSC). This strategy provides a simple and versatile platform for the design of new materials whose functionality can be easily modified. © 2011 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 49: 1147–1154, 2011

KEYWORDS: functionalization of polymers; differential scanning calorimetry; polyurethanes; sugar-based monomers; thermogravimetric analysis

INTRODUCTION The preparation and applications of polyurethanes have been extensively studied for the last few decades; these polymers have been mainly used as commodity materials and/or in industrial applications.[1] Similarly, the use of polyurethanes in biomedicine is being widely investigated due to their low toxicity, potential biodegradability, biocompatibility, and versatile structures.[2] Most of their applications are as plasticizer-free thermoplastic elastomers in the preparation of a wide range of medical devices, including thin-walled flexible tubing, catheters, surgical drains, intra-aortic balloon pumps, and so forth. Because of their excellent biocompatibility and low thrombogenicity, biodegradable polyurethanes can be used as nonpermanent devices.

The rational design of polymers tailored to exert distinct biological functions plays an important role in the development of controlled drug delivery systems. Thus, the controlled release of therapeutic molecules of both hydrophilic and hydrophobic drugs is achieved by anchoring the active agent to polymer structures by means of physical interactions or by covalent linkages.

Various hydroxyl-containing polymers have been synthesized for biomedical applications: for example, the anchorage of hemoglobin to a derivatized poly(ethylene glycol-*co*-lactic acid-*co*-polycaprolactone) was achieved by hydrogen-bond interactions with the amine, hydroxyl, and carboxylic acid moieties present in the polymer structure;[3] a carbonate-polyethylene glycol copolymer was also prepared as a drug carrier with tumor-targeting groups in its side chains.[4] Similarly, drug release systems based on poly(2-hydroxyethyl methacrylate) and poly(2-hydroxypropyl methacrylate) hydrogels were recently reported for use in ophthalmology.[5] In addition, Harada et al. reported the synthesis of a polyethylene glycol and polyaspartic acid block-copolymer, which can be used as drug carrier of the anticancer Docetaxel, covalently attached by ester bonds to the polymer chains.[6] Poly(β-amino esters) with pendant hydroxyl groups were proved to be good as gene delivery polymers as well.[7]

The modification of polymers after the successful achievement of a polymerization process is an important task in macromolecular science. Click chemistry (CC) may serve as a powerful strategy in its search. CC has emerged as a widespread approach that uses only the most-practical and -reliable chemical transformations, with an explosive growth in publications in recent years.[8–10] Although fitting the requirements of a click reaction is a tall order, several processes did so. Thus, the thiol-ene coupling reaction is a well-established click reaction that combines a thiol moiety and an alkene/alkyne group in a robust, efficient, and orthogonal method for the functionalization of different compounds.[11] Allyl groups can be used in thiol-ene coupling reactions as the "ene" part with great success.[12–14] Although allyl groups have been widely used as curing agents in polymer chemistry,[15–17] examples of linear soluble thermoplastic polymers with allyl pendant groups are scant.[18–20]

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The aim of this work was the synthesis of mono-, di-, and tri-*O*-allyl-L-arabinitol-based diol monomers useful for the preparation of well-established and systematically varied multifunctional polyurethanes with allyl pendant groups for later derivatization via CC. We have applied this method to the synthesis of a tri-*O*-allyl-L-arabinitol-based polyurethane which was later derivatized with 2-mercaptoethanol to get a highly hydroxylated material.

EXPERIMENTAL

Common reagents and solvents were purchased from Aldrich Chemical Co. and used as received. Solvents were dried and purified, when necessary, by appropriate standard procedures.

Optical rotations were measured in a Perkin-Elmer 341 polarimeter 20 ± 0.5 °C (1 dm cell). Elemental analyses were determined in the Microanalysis Laboratories of the CITIUS Service, in the University of Seville. IR spectra were recorded on a JASCO FT/IR-410 spectrometer. NMR spectra were recorded at 300 K on either a Bruker Advance AV-500 or a Bruker AMX-500 spectrometer. Chemical shifts (δ) are reported as parts per million downfield from Me_4Si. Mass spectra were obtained using a Kratos MS80RFA instrument. Gel permeation chromatography (GPC) analyses were performed using a Waters apparatus equipped with a Waters 2414 refractive-index detector and two Styragel® HR columns (7.8 × 300 mm^2) linked in series, thermostatted at 60 °C, using *N*-methylpyrrolidone as the mobile phase, at a flow rate of 0.5 mL min^{-1}. Molecular weights were estimated against polystyrene standards. The thermal behavior of the polyurethanes was examined by differential scanning calorimetry (DSC), using a Perkin-Elmer DSC-7 calorimeter calibrated with indium. DSC data were obtained from samples of 4–6 mg at heating/cooling rates of 10 °C min^{-1} under a nitrogen flow. The glass transition temperatures were determined at a heating rate of 20 °C min^{-1} from rapidly melt-quenched polymer samples. Thermogravimetric analyses were performed under nitrogen atmosphere (flow rate 100 mL min^{-1}) with a Universal V4.3A TA instrument at a heating rate of 10 °C min^{-1}.

The polymerization reactions were performed in absence of humidity, under inert atmosphere. All glassware was heated overnight at 80 °C before use, and after assembly was further heated under vacuum to eliminate the surface moisture. The diol monomer 2,3,4-tri-*O*-allyl-L-arabinitol (**ArAll$_3$, 4**) was dried under high vacuum for at least 3 days. 1,6-Hexamethylene diisocyanate (HMDI) was stored at 4 °C, and the diol monomer at room temperature—both were handled under inert atmosphere. *N,N*-Dimethylformamide (DMF) was used as polymerization solvent and was further dried to eliminate residual water. DMF was vacuum distilled and stored over molecular sieve in a desiccator for not more than a week before use. The other reactants and reagents for the polymerizations were stored in a desiccator under inert atmosphere until required.

Synthesis of Monomers

2,3,4-Tri-O-allyl-1,5-di-O-trityl-L-arabinitol (3)

To sodium hydride (60% w/w) (1.24 g, 31.1 mmol) washed with dry pentane (40 mL × 3) under argon atmosphere, a solution of the ditrityl compound **2** (6.00 g, 9.43 mmol) in dry tetrahydrofuran (THF) (50 mL) was added dropwise at 0 °C. The mixture was then stirred at 30 °C for 1 h, allyl bromide (2.7 mL, 31.1 mmol) was added, and the reaction proceeded overnight. Methanol (5 mL) was added dropwise, and the mixture was stirred for 1 h. The reaction mixture was evaporated to dryness, and the residue was dissolved in a 1:1 mixture of CH_2Cl_2 and H_2O (200 mL). The organic phase was washed with water (50 mL), dried (anhydrous $MgSO_4$), and evaporated to dryness. The residue was purified by column chromatography (1:9 *tert*-butylmethyl ether-hexane) to give the title compound as a white solid (5.10 g, 72%). M.p. (methanol) 65–66 °C. $[\alpha]_D$ +9.5° (*c* 1.0, $CHCl_3$). IR: ν (cm^{-1}) 3058, 3022 (C—H arom.), 1645 (C=C), 1071 (C—O—C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.12 (dd, 1H, H-5a, $J_{H\text{-}5a,H\text{-}4}$ = 4.4 Hz, $J_{H\text{-}5a,H\text{-}5b}$ =10.2 Hz), 3.23 (dd, 1H, H-1a, $J_{H\text{-}1a,H\text{-}2}$ = 6.7 Hz, $J_{H\text{-}1a,H\text{-}1b}$ =9.5 Hz), 3.40 (dd, 1H, H-1b, $J_{H\text{-}1b,H\text{-}2}$ =5.4 Hz, J = 9.5 Hz), 3.48 (dd, 1H, H-5b, $J_{H\text{-}5b,H\text{-}4}$ = 2.4 Hz, J = 10.2 Hz), 3.65 (ddd, 1H, H-4, J = 2.4 Hz, J = 4.4 Hz, $J_{H\text{-}3,H\text{-}4}$ = 7.8 Hz), 3.76–3.80 (m, 2H, 2C$\underline{H}_2$CH=), 3.82–3.85 (m, 1H, H-2), 3.92 (dd, 1H, H-3, $J_{H\text{-}2,H\text{-}3}$ =3.1 Hz, J = 7.8 Hz), 3.95–4.01; 4.12–4.16; 4.23–4.27 (m, 4H, 2C$\underline{H}_2$CH=), 4.81–4.86; 5.10–5.12; 5.20–5.23; 5.33–5.36 (m, 6H, 3C$\underline{H}_2$=), 5.37–5.45; 5.85–5.92; 5.98–6.06 (m, 3H, 3C$\underline{H}$=), 7.23–7.51 (m, 30H, Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 62.3 (C-5), 62.7 (C-1), 71.4, 72.3, 73.6 (3C, 3C$\underline{H}_2$CH=), 77.6 (C-3), 77.9 (C-2/C-4), 86.4, 86.9 (2C, C$\underline{Ph}_3$), 116.4, 116.6 (3C, $\underline{C}H_2$=), 126.8, 127.0, 127.7, 127.8, 128.7, 128.8, 144.0, 144.1 (Ph), 135.0, 135.1, 135.3 (3C, CH=).

HRFABMS: Calculated molecular weight for $C_{52}H_{52}O_5Na$ $(M + Na)^+$ 779.3705; experimental molecular weight: 779.3712.

Anal. Calcd. for ($C_{52}H_{52}O_5$): C, 82.51, H, 6.92. Found: C, 82.55, H, 7.14.

3,4-Di-O-allyl-1,5-di-O-trityl-L-arabinitol (5)

This was obtained from 1,5-ditrityl-L-arabinitol **2** following the procedure described previously for **3** at 20 °C. The amounts used were the following: compound **2** (3.80 g, 5.97 mmol), sodium hydride (60% w/w) (0.48 g, 20.1 mmol) and allyl bromide (1.0 mL, 11.9 mmol) in THF (30 mL). The reaction was worked up as mentioned above, and the residue was purified by column chromatography (1:5 *tert*-butylmethyl ether-hexane) to give the title compound as a white solid (2.6 g, 60% yield). M.p. (1:1, diethyl ether-hexane) 60–61 °C. $[\alpha]_D$ + 11.0° (*c* 1.0, $CHCl_3$). IR ν (cm^{-1}) 3286 (O—H), 3057, 3022 (C—H arom.), 1646 (C=C), 1069 (C—O—C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.01 (d, 1H, OH, $J_{OH,H\text{-}2}$ = 6.2 Hz), 3.23 (dd, 1H, H-5a, $J_{H\text{-}5a,H\text{-}4}$ = 6.5 Hz, $J_{H\text{-}5a,H\text{-}5b}$ = 9.4 Hz), 3.30–3.35 (m, 2H, H-1), 3.39 (dd, 1H, H-5b, $J_{H\text{-}5b,H\text{-}4}$ = 5.6 Hz, J = 9.4 Hz), 3.78–3.83 (m, 4H, H-3/H-4/1C$\underline{H}_2$CH=), 3.99–4.04 (m, 1H, H-2), 3.87–3.91; 4.08–4.11 (m, 2H, 1C$\underline{H}_2$CH=), 4.96–5.00; 5.11–5.22 (m, 4H, 2C$\underline{H}_2$=), 5.51–5.59; 5.79–5.87 (m, 2H, 2C$\underline{H}$=), 7.23–7.53 (m, 30$\underline{H}$, Ph). ^{13}C NMR

($CDCl_3$, 125 MHz): δ (ppm) 62.4 (C-5), 64.5 (C-1), 70.2 (C-2), 72.1, 72.6 (2C, $\underline{C}H_2CH$=), 77.5 (C-3), 77.7 (C-4), 86.8, 86.9 (2C, $\underline{C}Ph_3$), 117.1, 117.6 (2C, CH_2=), 127.0, 127.1, 127.8, 127.9, 128.6, 128.7, 143.8, 143.9 (Ph), 134.8 (2C, CH=). MS (CI): m/z 739 $(M + Na)^+$, 243 $(Ph_3C)^+$, 91 $(C_7H_7)^+$.

Anal. Calcd. for ($C_{49}H_{48}O_5$): C, 82.09, H, 6.75. Found: C, 81.93, H, 6.52.

4-O-Allyl-1,5-di-O-trityl-L-arabinitol (8)

This was obtained from 1,5-ditrityl-L-arabinitol **2** following the procedure described previously for **3** at 20 °C. The amounts used were the following: compound **2** (2.50 g, 3.93 mmol), sodium hydride (60% w/w) (0.17 g, 4.32 mmol) and allyl bromide (0.34 mL, 3.97 mmol) in THF (20 mL). The reaction was worked up as mentioned above, and the residue was purified by column chromatography (1:5 *tert*-butylmethyl ether-hexane) to give the title compound as a white solid (1.39 g, 52% yield). M.p. (1:1, diethyl ether-hexane) 70–71 °C. $[\alpha]_D$ +4.0° (c 1.0, $CHCl_3$). IR: ν (cm^{-1}) 3565 (O—H), 3057, 3022 (C—H arom.), 1596 (C=C), 1068 (C—O—C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.46 (d, 1H, OH, J = 7.5 Hz), 2.62 (d, 1H, OH, J = 6.1), 3.27–3.39 (m, 4H, H-1/H-5), 3.69–3.81 (m, 3H, H-2/H-3/H-4), 3.90–3.94; 4.13–4.17 (m, 2H, $C\underline{H}_2CH$=), 5.11–5.20 (m, 2H, CH_2=), 5.80–5.87 (m, 1H, CH=), 7.16–7.45 (m, 30H, Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 63.9, 64.9 (C-1/C-5), 71.0, 72.1, 76.7 (C-2/C-3/C-4), 72.0 ($C\underline{H}_2CH$=), 86.8, 87.1 (2C, $\underline{C}Ph_3$), 117.2 (CH_2=), 127.0, 127.1, 127.8, 127.9, 128.6, 128.7, 143.8, 143.9 (Ph), 134.7 (CH=). MS (CI): m/z 699 $(M + Na)^+$, 243 $(Ph_3C)^+$, 91 $(C_7H_7)^+$.

Anal. Calcd. for ($C_{46}H_{44}O_5$): C, 81.63, H, 6.55. Found: C, 81.48, H, 6.58.

3,4-Di-O-allyl-2-O-methyl-1,5-di-O-trityl-L-arabinitol (6)

To sodium hydride (60% w/w) (0.07 g, 1.7 mmol) washed with dry pentane (20 mL × 3) under argon atmosphere, a solution of **5** (0.80 g, 1.10 mmol) in dry THF (15 mL) was added dropwise at 0 °C. The mixture was then heated at 30 °C for 1 h, methyl iodide (80 μL, 1.21 mmol) was added, and stirring was continued overnight. Methanol (1 mL) was added dropwise, and the suspension was stirred for 1 h. The reaction mixture was evaporated to dryness, and the residue was then dissolved in a 1:1 mixture of CH_2Cl_2 and H_2O (80 mL). The organic phase was washed with water (10 mL), dried (anhydrous $MgSO_4$), and evaporated to dryness. The residue was purified by column chromatography (1:14 *tert*-butylmethyl ether-hexane) to give the title compound as a white solid (0.75 g, 94%). M.p. (methanol) 58–59 °C. $[\alpha]_D$ +13.5° (c 1.0, $CHCl_3$). IR: ν (cm^{-1}) 3057, 3031 (C—H arom.), 1595 (C=C), 1070 (C—O—C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.10 (dd, 1H, H-5a, $J_{H\text{-}5a,H\text{-}4}$ =3.8 Hz, $J_{H\text{-}5a,H\text{-}5b}$ = 10.0 Hz), 3.18 (dd, 1H, H-1a, $J_{H\text{-}1a,H\text{-}2}$ = 7.0 Hz, $J_{H\text{-}1a,H\text{-}1b}$ =9.4 Hz), 3.40 (dd, 1H, H-1b, $J_{H\text{-}1b,H\text{-}2}$ =5.2 Hz, J = 9.4 Hz), 3.47 (s, 3H, CH_3), 3.47–3.53 (m, 2H, H-5b/H-4), 3.74–3.76 (m, 2H, $1C\underline{H}_2CH$=), 3.89–3.91 (m, 2H, H-2/H-3), 4.00–4.03; 4.14–4.17 (m, 2H, $1C\underline{H}_2CH$=), 4.77–4.83 (m, 2H, $C\underline{H}_2$=), 5.12-5.26 (m, 2H, $C\underline{H}_2$=), 5.34–5.39 (m, 1H, C$\underline{H}$=), 5.88–5.93 (m, 1H, C$\underline{H}$=), 7.24–7.51 (m, 30H, Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 58.1 (CH_3), 61.6, 62.4 (C-1/C-5), 72.4, 73.6 (2C, $\underline{C}H_2CH$=), 77.4, 77.6, 79.7 (C-2/C-3/C-4), 86.4, 86.9 (2C, $\underline{C}Ph_3$), 116.6, 116.8 (2C, CH_2=), 126.9, 127.0, 127.7, 127.8, 128.7, 128.8, 144.0, 144.1 (Ph), 134.9, 135.3 (2C, CH=).

HRFABMS: Calculated molecular weight for $C_{50}H_{50}O_5Na$ $(M + Na)^+$ 753.3572; experimental molecular weight: 753.3556.

4-O-Allyl-2,3-di-O-methyl-1,5-di-O-trityl-L-arabinitol (9)

This was obtained by methylation of compound **8** following the procedure described previously for compound **6**. The amounts used were the following: allyl derivative **8** (0.80 g, 1.18 mmol), sodium hydride (60% w/w) (0.11 g, 2.60 mmol) and methyl iodide (0.15 mL, 2.38 mmol) in THF (20 mL). The reaction was worked up as mentioned above, and the residue was purified by column chromatography (1:9 *tert*-butylmethyl ether-hexane) to give the title compound as a white solid (1.75 g, 90% yield). M.p. (methanol) 58–59 °C. $[\alpha]_D$ +14.0° (c 1.0, $CHCl_3$). IR: ν (cm^{-1}) 3058, 3022 (C—H arom.), 1596 (C=C), 1073 (C—O—C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.08–3.10 (m, 4H, CH_3/H-1a), 3.18 (dd, 1H, H-5a, $J_{H\text{-}5a,H\text{-}4}$ = 7.4 Hz, $J_{H\text{-}5a,H\text{-}5b}$ = 9.3 Hz), 3.41 (dd, 1H, H-5b, $J_{H\text{-}5b,H\text{-}4}$ = 5.4 Hz, J = 9.3 Hz), 3.43–3.45 (m, 1H, H-2), 3.46 (s, 3H, CH_3), 3.49 (dd, 1H, H-1b, $J_{H\text{-}1b,H\text{-}2}$ = 2.2 Hz, $J_{H\text{-}1a,H\text{-}1b}$ = 10.2 Hz), 3.75 (dd, 1H, H-3, $J_{H\text{-}3,H\text{-}4}$ = 2.6 Hz, $J_{H\text{-}2,H\text{-}3}$ = 8.2 Hz), 3.85 (ddd, 1H, H-4, J = 2.6 Hz, J = 5.4 Hz, J = 7.4 Hz), 3.96–4.00; 4.11–4.15 (m, 2H, $C\underline{H}_2CH$=), 5.12–5.25 (m, 2H, CH_2=), 5.85–5.93 (m, 1H, CH=), 7.23–7.53 (m, 30H, Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 58.0, 60.7 (2C, CH_3), 61.7 (C-1), 62.3 (C-5), 72.3 ($C\underline{H}_2CH$=), 77.5 (C-4), 79.7 (C-3), 79.8 (C-2), 86.5, 86.9 (2C, $\underline{C}Ph_3$), 116.7 (CH_2=), 126.9, 127.0, 127.7, 127.8, 128.7, 128.8, 144.1, 144.2 (Ph), 135.3 (2C, CH=).

HRFABMS: Calculated molecular weight for $C_{48}H_{48}O_5Na$ $(M + Na)^+$ 727.3399; experimental molecular weight: 727.3378.

2,3,4-Tri-O-allyl-L-arabinitol (ArAll$_3$, 4)

Silica gel (3 g), activated by perchloric acid,[21] was added to a solution of **3** (2.00 g, 2.64 mmol) in methanol (50 mL), and the reaction mixture was stirred at 25 °C for 5 h. Silica was filtered off, and the resulting solution was concentrated to dryness. The residue was purified by column chromatography (1:5 *tert*-butylmethyl ether-hexane) to give the title compound as a colorless oil (0.60 g, 84%). $[\alpha]_D$ −1.0° (c 1.0, $CHCl_3$). IR: ν (cm^{-1}) 3420 (O—H), 3078 (C—H vinyl), 1646 (C=C), 1063 (C—O—C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.34 (dd, 1H, OH, J = 5.6 Hz, J = 7.2 Hz), 2.37 (dd, 1H, OH, J = 4.9 Hz, J = 7.4 Hz), 3.63–3.67 (m, 2H, H-2/H-4), 3.72 (dd, 1H, H-3, J = 4.6 Hz, J = 5.7 Hz), 3.76–3.89 (m, 4H, H-1/H-5), 4.08–4.26 (m, 6H, $3C\underline{H}_2CH$=), 5.20–5.24; 5.29–5.31; 5.33–5.34 (m, 6H, $3C\underline{H}_2$=), 5.91–6.00 (m, 3H, 3C$\underline{H}$=). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 60.7, 61.5 (C-1/C-5), 71.0, 71.8, 73.5 (3C, CH_2CH=), 79.0, 79.1, 79.2 (C-2/C-3/C-4), 117.3, 117.4, 117.5 (3C, CH_2=), 134.2, 134.6, 134.8 (3C, CH=). MS (CI): m/z 273 $(M + 1)^+$, 57 $(OAll)^+$.

Anal. Calcd. for ($C_{14}H_{24}O_5$): C, 61.74, H, 8.88. Found: C, 61.58, H, 8.50.

3,4-di-O-allyl-2-O-methyl-L-arabinitol (ArAll$_2$, 7)

This was obtained from **6** following the procedure described above for **4**. The amounts used were the following: dityrityl derivative **6** (0.50 g, 0.68 mmol), and activated silica (0.75 g) in methanol (10 mL). The reaction was worked up as mentioned above, and the residue was purified by column chromatography (2:1 dichloromethane-*tert*-butylmethyl ether) to give the title compound as an oil (0.15 g, 90% yield). $[\alpha]_D$ −3.5° (*c* 1.0, $CHCl_3$). IR: *v* (cm^{-1}) 3414 (O—H), 1645 (C=C), 1073 (C—O—C). ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.41 (bs, 1H, OH), 2.46 (bs, 1H, OH), 3.41–3.48; 3.55–3.62 (m, 5H, CH_3/H-2/H-4), 3.64–3.68 (m, 1H, H-3), 3.69–3.87 (m, 4H, H-1/H-5), 4.02–4.22 (m, 4H, $2CH_2CH$=), 5.14–5.20; 5.24–5.31 (m, 4H, $2CH_2$=), 5.87–5.97 (m, 2H, 2CH=). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 57.5 (CH_3), 59.9, 61.5 (C-1/C-5), 71.9, 73.5 (2C, $2CH_2CH$=), 78.6, 78.7, 80.9 (C-2/C-3/C-4), 117.4, 117.5 (2C, CH_2=), 134.6, 134.7 (2C, CH=).

HRFABMS: Calculated molecular weight for $C_{12}H_{22}O_5Na$ $(M + Na)^+$ 269.1365; experimental molecular weight: 269.1362.

4-O-Allyl-2,3-di-O-methyl-L-arabinitol (ArAll$_1$, 10)

This was obtained from **9** following the procedure described previously for **4**. The amounts used were the following: dityrityl derivative **9** (0.50 g, 0.71 mmol), activated silica (0.75 g), and methanol (15 mL). The reaction was worked up aforementioned, and the residue was purified by column chromatography (*tert*-butylmethyl ether) to give the title compound as an oil (0.15 g, 96% yield). $[\alpha]_D$ −0.5° (*c* 1.0, $CHCl_3$). IR: *v* (cm^{-1}) 3397 (O—H), 1646 (C=C), 1075 (C—O—C). ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.33 (t, 1H, OH, J = 5.7 Hz), 2.39 (t, 1H, OH, J = 5.2 Hz), 3.44–3.46; 3.51–3.54 (m, 2H, H-2/H-3), 3.47 (s, 3H, CH_3), 3.55 (s, 3H, CH_3), 3.61–3.66 (m, 1H, H-4), 3.73–3.93 (m, 4H, H-1/H-5), 4.12–4.16; 4.21–4.25 (m, 2H, CH_2CH=), 5.21–5.22; 5.23–5.24; 5.30–5.31; 5.34–5.35 (m, 2H, CH_2=), 5.93–6.02 (m, 1H, CH=). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 57.5, 60.6 (2C, CH_3), 59.8, 61.5 (C-1/C-5), 71.9 (CH_2CH=), 79.0 (C-4), 80.7, 81.2 (C-2/C-3), 117.4 (CH_2=), 134.8 (CH=).

HRFABMS: Calculated molecular weight for $C_{10}H_{20}O_5$: $(M)^+$ 221.1389; experimental molecular weight: 221.1386.

Polymerization and Thiol-Ene Coupling Reactions

Polyurethane PU(ArAll$_3$-HMDI) (12)

The diol monomer $ArAll_3$ **(4)** (0.18 g, 0.67 mmol) was loaded in a round-bottom flask with an argon/vacuum inlet. The system was treated with three cycles of vacuum-argon before the addition, via cannula, of dried DMF (5 mL). The mixture was stirred to homogenization, and the diisocyanate (HMDI, 0.11 mL, 0.67 mmol) was added under argon atmosphere, followed by the catalyst (dibutyltin dilaurate, one drop). The polymerization solution was stirred at 60 °C for 5 h under argon atmosphere. Triethylene glycol (0.2 mL) was added, the mixture was stirred for 30 min, and the solution was added dropwise into cold diethyl ether (250 mL), where the polymer PU($ArAll_3$-HMDI) precipitated. The polyurethane was purified by redissolution in a small volume of chloroform (2 mL) and reprecipitation in diethyl ether. The pure polymer (white solid) was dried under vacuum for 2 days and stored in a desiccator (0.27 g, 91% yield). M_w 13000; M_n 8700; M_w/M_n 1.5. IR: *v* (cm^{-1}) 3325 (N–H), 3078 (C–H vinyl), 1695 (C=O urethane), 1529 (N–H, N–C=O, urethane), 1245 (C—N). ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 1.33 (bs, 4H, CH_2-h), 1.49 (bs, 4H, CH_2-g), 3.15 (bs, 4H, CH_2-f), 3.57–3.83 (m, 3H, H-2/H-3/H-4), 3.96–4.52 (m, 10H, $3CH_2CH$=/H-1/H-5), 4.98 (bs, 2H, 2NH), 5.12–5.30 (m, 6H, $3CH_2$=), 5.84–5.94 (m, 3H, 3CH=). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 26.3 (CH_2-h), 29.8 (CH_2-g), 40.9 (CH_2-f), 62.6, 63.6 (C-1/C-5), 71.0, 72.4, 73.9 (3C, CH_2CH=) 76.2, 78.4 (C-2/C-3/C-4), 117.1, 117.2, 117.3 (3C, CH_2=), 134.5, 134.6, 134.9 (3C, CH=), 156.2, 156.4 (C=O). Anal. Calcd. for ($C_{22}H_{36}N_2O_7$): C, 59.28, H, 8.24, N, 6.36. Found: C, 59.27, H, 8.16, N, 6.26.

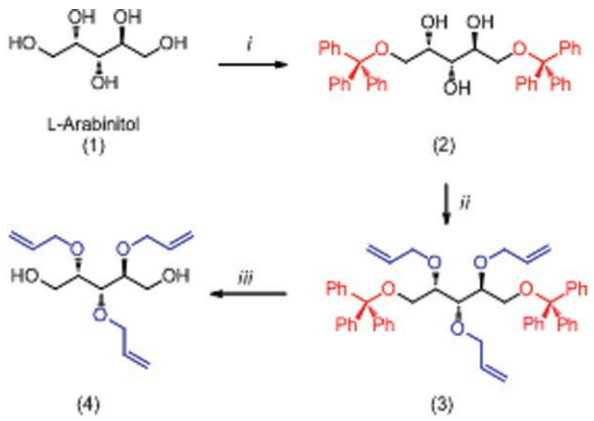
2,3,4-Tri-O-[3-(2-hydroxyethylthio)propyl]-1,5-di-O-trityl-L-arabinitol (11)

2,3,4-Tri-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol (**3**, 0.20 g, 0.26 mmol) was dissolved in DMF (2 mL). The solution was degassed, and 2-mercaptoethanol (1.1 mL, 15.6 mmol) and 2,2′-azobisisobutyronitrile (AIBN) as radical initiator (0.13 g; 0.78 mmol) were added under argon atmosphere. The solution was stirred at 80 °C for 24 h. The reaction mixture was then poured into cold water (30 mL) and extracted with dichloromethane (3 x 50 mL). Sodium chloride was occasionally added—when needed—to break the emulsion. The combined organic layers were dried (anhydrous sodium sulfate) and evaporated to dryness to give a slightly colored residue. Purification was achieved by column chromatography (1:2 *tert*-butylmethyl ether-hexane) to give the title compound as an uncolored oil (0.23 g, 89 % yield). $[\alpha]_D$ +1.0° (*c* 1.0, $CHCl_3$). IR: *v* (cm^{-1}) 3395 (O—H), 3056 (C—C arom.), 1066 (C—O—C). ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 1.39–1.45 (m, 2H, $1CH_2$-d), 1.83 (m, 2H, $1CH_2$-d), 1.90–2.00 (m, 2H, $1CH_2$-d), 2.17–2.20 (m, 2H, $1CH_2$-c), 2.38 (bs, 2H, 2OH), 2.43 (bs, 1H, OH), 2.55–2.62; 2.67–2.70 (m, 8H, $2CH_2$-b/$2CH_2$-c), 2.76 (t, 2H, CH_2-b, JCH_2-b,CH_2-a = 6.0 Hz), 3.09 (dd, 1H, H-5a, J_{H5a-H4} = 4.9 Hz, $J_{H5a-H5b}$ = 10.2 Hz), 3.22–3.79 (m, 18H, $3CH_2$-a/$3CH_2$-e/H-1/H-2/H-3/H-4/H-5b), 7.24-7.51 (m, 30H, Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 28.2, 28.6, 28.7 (3C, CH_2-c), 30.3, 30.4, 30.5 (3C, CH_2-d), 35.0, 35.2, 35.3 (3C, CH_2-b), 60.4, 60.5, 60.6, 69.0, 69.5, 71.0 (6C, $3CH_2$-a/$3CH_2$-e), 62.5, 62.6 (C-1/C-5), 78.8, 78.7, 78.6 (C-2/C-3/C-4), 86.6, 87.0 (2C, Ph_3C), 127.0, 127.1, 127.7, 127.8, 128.7, 128.8, 144.0, 144.1 (Ph).

HRFABMS: Calculated molecular weight for $C_{58}H_{70}O_8NaS_3$ $(M + Na)^+$ 1013.4131; experimental molecular weight: 1013.4118.

Polyurethane PU[Ar(S-OH)$_3$-HMDI] (13)

This was obtained from PU($ArAll_3$-HMDI) **(12)** following the procedure described previously for **11**. The amounts used were the following: PU($ArAll_3$-HMDI) (0.05 g, 0.11 mmol), DMF (1 mL), and AIBN (0.11 g; 0.66 mmol). The reaction was worked up by precipitation over diethyl ether to give the title polyurethane as a slightly colored syrup (0.07 g, 91% yield). M_w 14900; M_n 8100; M_w/M_n 1.8. IR: *v* (cm^{-1}) 3319 (O—H, N—H urethane), 1695 (C=O urethane), 1536 (N—H, N—C=O, urethane), 1253 (C—N). ^1H NMR (DMSO-d_6, 500 MHz): δ (ppm) 1.25 (bs, 4H, CH_2-h), 1.40 (bs, 4H, CH_2-g), 1.72 (bs, 6H, CH_2-d) 2.56 (bs, 12H, CH_2-b/CH_2-c), 2.97



SCHEME 1 Synthesis of 2,3,4-tri-*O*-allyl-L-arabinitol **4**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(bs, 4H, CH_2-f), 3.38–3.84 (m, 15H, H-2/H-3/H-4/CH_2-a/CH_2-e), 3.84–4.00; 4.01–4.21; 4.22–4.41 (m, 4H, H-1/H-5), 4.74 (bs, 3H, 3OH), 7.10 (bs, 2H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 28.7 (CH_2-h), 31.1 (C-c/C-b), 32.3 (CH_2-g), 33.0 (C-d) 43.1 (CH_2-f), 63.6 (C-a/C-e), 65.9 (C-1/C-5), 71.9, 72.6, 73.4 (C-2/C-3/C-4), 157.2 (C=O). Anal. Calcd. for ($C_{28}H_{54}N_2S_3O_{10}$): C, 49.83, H, 8.06, N, 4.15, S, 14.25. Found: C, 50.02, H, 7.84, N, 4.07, S, 14.10.

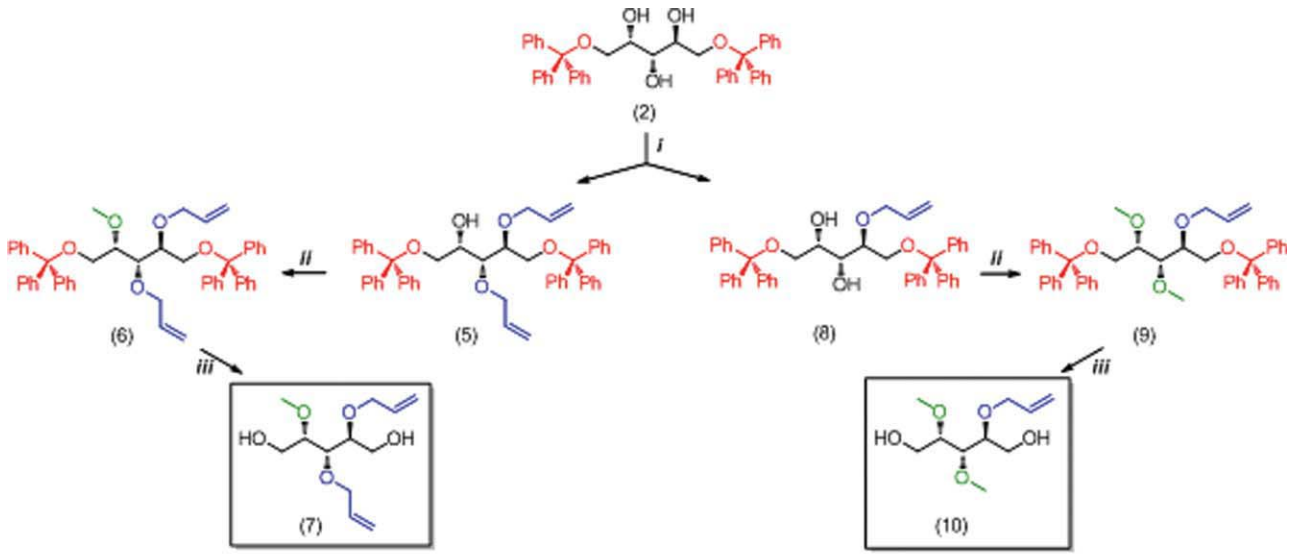
RESULTS AND DISCUSSION

Synthesis and Characterization of Monomers

In this study, the commercially available L-arabinitol (**1**) was the starting material for the synthesis of functional allyl diol monomers **4**, **7**, and **10**, which may be useful in the preparation of great numbers of chemically diverse polyurethanes by means of subsequent thiol-ene coupling reactions. The synthesis of the diol monomer 2,3,4-tri-*O*-allyl-L-arabinitol (**4**) was accomplished following the synthetic Scheme 1. 3,4-Di-*O*-allyl-2-*O*-methyl-L-arabinitol ($ArAll_2$, **7**) and 4-*O*-allyl-2,3-di-*O*-methyl-L-arabinitol ($ArAll_1$, **10**) were prepared according to Scheme 2. The structures of synthesized compounds and polymers have been elucidated on the basis of FTIR spectra, MS data, as well as 1D- and 2D-NMR experiments [(1)H, (13)C, COSY, NOESY, DEPT, and HSQC)].

For the preparation of $ArAll_3$ (**4**), a general protection–deprotection strategy was followed. Thus, primary hydroxyl groups of L-arabinitol (**1**) were blocked as trityl derivatives by reaction with trityl chloride in pyridine, at 25 °C, to give 1,5-di-*O*-trityl-L-arabinitol (**2**).[22] The per-allylation of compound **2** was accomplished using sodium hydride and allyl bromide in dry THF, to generate 2,3,4-tri-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol **3**. A good control of the reaction temperature (30 °C) was needed to achieve high yields. Significant amounts of partially substituted compounds 3,4-di-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol (**5**) and 4-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol (**8**) were formed when the reaction proceeded at 20 °C or below. Trityl groups were then removed in compound **3** by means of acid-mediated lyses, to give the triallyl diol $ArAll_3$ (**4**) in good yields (84%).

In the preparation of tailor-made polyurethanes with varied degrees of functionalization, the use of monoallyl, diallyl, or triallyl diol monomers accurately controls the amount of reactive pendant groups incorporated into the polymer backbone. Therefore, the synthesis of diallyl and monoallyl by-products (**5** and **8**, respectively) in good yields was undertaken next. After treatment of **2** with sodium hydride, the reaction temperature was kept below 20 °C to enhance the



SCHEME 2 Synthesis of diallyl and monoallyl diol monomers (**7** and **10**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

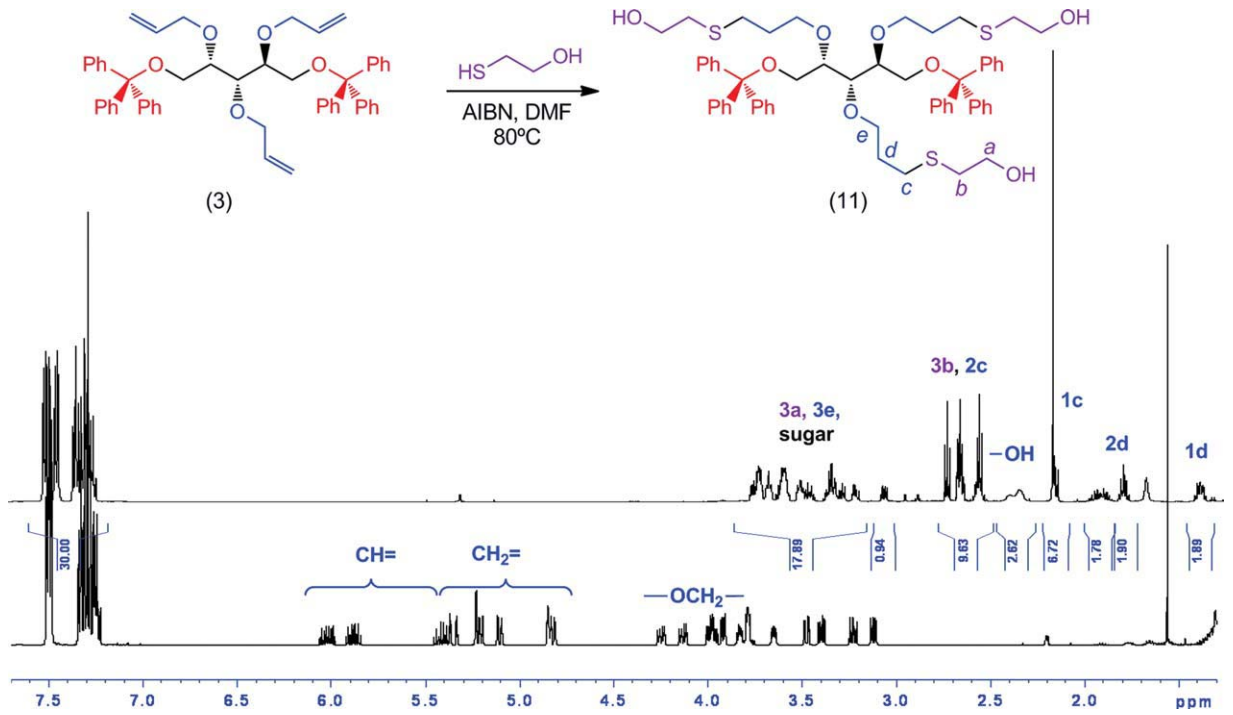


FIGURE 1 ^{1}H NMRs of compound **11** (top spectrum) synthesized from compound **3** (bottom trace).

chemoselectivity of allyl bromide toward the free hydroxyl groups; thus, first the hydroxyl group at carbon 4 was substituted (rendering the monoallyl compound **8**), followed by the hydroxyl group at carbon 3 (to give the diallyl product **5**).

The diallyl functionalization of dityrityl **2** to give compound **5** was confirmed by complete NMR characterization using COSY, HSQC, DEPT, and NOESY experiments, and its structure was unequivocally resolved. Thus, compound **5** bears a free hydroxyl group on carbon 2, and an allyl ether moiety on each of carbons 3 and 4. Homonuclear 2D-COSY experiments revealed that the unsubstituted —OH group (d, 1H, 3.01 ppm) was coupled with a signal at 3.99–4.04 ppm (m, 1H, H-2), which in turn can be correlated with an Ha-Hb system at 3.30–3.35 ppm (m, 2H, H-1a and H-1b). The assignation of H-2 was carried out by NOESY experiments. As the planar, zigzag arrangement must be the preponderant conformation in solution for the carbohydrate skeleton of **5**,[23–25] the spatial correlation of H-2 with H-3 confirms this assignation.

Free secondary hydroxyl groups in compounds **5** and **8** needed to be blocked to avoid crosslinking reactions in polymer synthesis. Their protection as methyl ether gave compounds **6** and **9** in excellent yields (>90%), followed by acid-mediated detritylation to render the diol monomers 3,4-di-*O*-allyl-2-*O*-methyl-L-arabinitol ($ArAll_2$, **7**) and 4-*O*-allyl-2,3-di-*O*-methyl-L-arabinitol ($ArAll_1$, **10**).

Thiol-ene Reaction

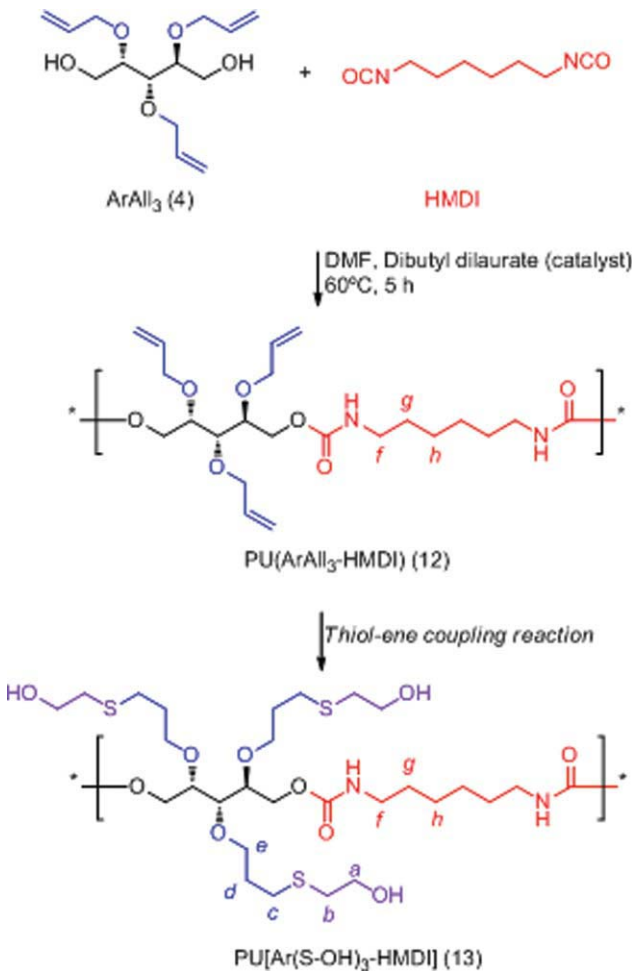
The thiol-ene reaction shows all the desirable features of a click reaction, that is, it is highly efficient, simple to execute with no side products, and proceeds rapidly to high yields.[11] This reaction was implemented in various synthetic methods, including surface and polymer modification; its unique spatial and temporal control of the click reaction resulted in well-defined, highly uniform polymer structures.

So we have investigated the derivatization of a novel polyurethane via thiol-ene chemistry. 2-Mercaptoethanol was the thiol of choice in the present study because of its simple and convenient chemical structure. The reaction was firstly studied on sugar precursors. Therefore, 2,3,4-tri-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol (**3**) was used to resemble the great steric hindrance that can be expected in the polymer backbone. An excess of 2-mercaptoethanol was used to ensure a complete addition to every allyl group. The reaction was conducted in DMF, and oxygen was removed via argon bubbling. The trial was thermally initiated by AIBN, leading to compound **11** in high yields. In spite of the significant steric hindrance exerted by the two trityl groups in the tri-*O*-allyl derivative (**3**), total functional group conversion was achieved. Figure 1 displays the reaction scheme and the ^{1}H-NMR spectra of both the starting material **3** and the final compound **11**. Of note in the upper spectrum is the complete disappearance of signals from the vinyl protons (4.7–6.2 ppm) and the appearance of the peaks corresponding to the —OH groups (3H, 2.43 ppm) and to the *a, b, c*, and *d* methylene groups present in the final compound.

As far as we are aware, this method has not previously been used in polyurethane chemistry. Consequently, its development may be a new approach to well-defined reactive polyurethanes useful for a variety of biomedical and nanotechnological applications.

Synthesis and Characterization of Polymers

The thiol-ene method was applied to the synthesis of a novel linear polyurethane. This method can be used for the



SCHEME 3 Polymerization reaction of compound **4** with HMDI and subsequent thiol-ene coupling reaction with 2-mercaptoethanol. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

preparation of polyurethanes with enhanced properties, namely higher hydrophilicity, increased wettability, improved biodegradation behavior, and the preparation of highly functionalized polymers such as polyanionic and polycationic materials, and so forth through the combination of different thiols and multi-ene polymers.

The precursor polymer PU($ArAll_3$-HMDI) (**12**) was prepared by reaction of 2,3,4-tri-*O*-allyl-L-arabinitol ($ArAll_3$, **4**) with HMDI (Scheme 3). The polymerization took place under argon atmosphere at 60 °C in DMF for 5 h to ensure the total consumption of diol monomer. The recovered multiallyl polyurethane **12** was isolated by precipitation in diethyl ether with excellent yields (>90%), and subsequently subjected to the click reaction, where the thiol used was 2-mercaptoethanol. The reaction conditions were similar to those described for the preparation of compound **11**, and the reaction was allowed to proceed for 24 h, with complete coupling of thiol fragments to every allyl moiety, giving the novel polyhydroxylated polymer PU[($Ar(S\text{-}OH)_3$-HMDI] (**13**).

Both new polymers were fully characterized by FTIR, NMR, and GPC, and their thermal properties were also studied. Molecular weights, polydispersities, and thermal properties of polyurethanes are shown in Table 1. Although the thiol-ene reaction carried out on PU($ArAll_3$-HMDI) (**12**) did not increase the average length of polymer chains, it was expected to increase the hydrodynamic volume; hence, PU[($Ar(S\text{-}OH)_3$-HMDI] **13** exhibited an augmented weight average molecular weight (M_w) and polydispersity (M_w/M_n) calculated by GPC compared with polyurethane **12**.

The thermal analysis of the new polyurethanes showed that they were stable to thermal degradation up to 200 °C (Fig. 2); the presence of {3-[(2-hydroxyethyl)thio]propyl} fragments in **13** had a marked effect on the degradation profile compared with allyloxy pendant groups in **12**, that is, those groups shifted the decomposition onset temperature from 280 to 239 °C, with an associated 10% weight loss (T_d^0), leading to materials of lower thermal resistance. Moreover, the degradation profile of polyurethane **13** displays other major differences with that of polymer **12**: first, the main degradation peak (275 °C, 43% weight loss) comes out at lower temperature than in polymer **12** (318, 78% weight loss); second, the degradation step at 455 °C—probably associated with the allyloxy groups in polymer **12**—was not observed.

Thermal transitions associated to melting were not observed in the DSC studies of polymers **12** and **13**. This behavior reveals that the materials are mainly amorphous. Both polymers showed low T_g values (16 °C and 9 °C, respectively) in

TABLE 1 Molecular Weights and Thermal Properties of Synthesized Polyurethanes

	GPC		DSC		TGA		
Polymer	M_w[a]	M_w/M_n[a]	T_m[b]	T_g[c]	T_d^0[d]	T_d[e]	ΔW (%)[f]
PU($ArAll_3$-HMDI)	13,000	1.5	–	16	280	318/455	78/18
PU[$Ar(S\text{-}OH)_3$-HMDI]	14,900	1.8	–	9	239	275/300	46/37

[a] Determined by GPC analysis against polystyrene standards using NMP as mobile phase.
[b] First heating (10 °C/min).
[c] Second heating (20 °C/min) after quenching from melting to −40 °C.
[d] Onset of decomposition (°C).
[e] Decomposition temperatures (°C) measured at the peaks of the derivative curves; major peaks in bold.
[f] Weight loss at the end of the decomposition step.

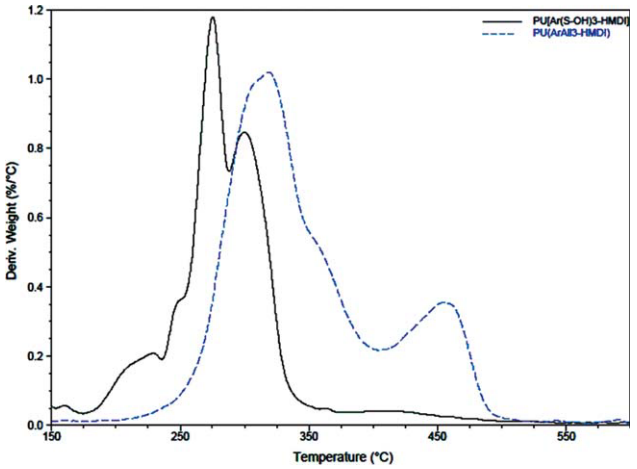


FIGURE 2 Comparative curves of thermal degradations under inert atmosphere of PU($ArAll_3$-HMDI) and PU[$Ar(S\text{-}OH)_3$-HMDI] homopolymers. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

agreement with the flexibility of their chains, suggesting that the allylated polymer is stiffer than the 2-hydroxyethylated one.

CONCLUSIONS

Three new diols—mono-, di-, and tri-*O*-allyl-L-arabinitol derivatives—have been successfully synthesized as intermediates for the preparation via CC of well-established and systematically varied polyurethanes with diverse degrees of functionalization. NMR characterization of the *O*-allyl derivatives obtained from 1,5-di-*O*-trityl-L-arabinitol (**2**) confirmed that first the hydroxyl group on C-4 was substituted [rendering 4-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol (**8**)], followed by the hydroxyl group on C-3 [to give 3,4-di-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol (**5**)] and, finally, by the hydroxyl group on C-2 [leading to 2,3,4-tri-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol (**3**)].

The thiol-ene coupling reaction between 2,3,4-tri-*O*-allyl-1,5-di-*O*-trityl-L-arabinitol (**3**) and 2-mercaptoethanol was firstly used as testing assay, and conversion of every allyl group was achieved. This method was later applied to the synthesis of a novel linear polyhydroxylated polyurethane. The precursor polymer PU($ArAll_3$-HMDI) (**12**) was subjected to the click reaction with complete coupling of thiol fragments to every allyl group. Both polyurethanes are amorphous and thermally stable up to 239 °C.

This method may be a new approach to well-defined reactive polyurethanes useful for a variety of biomedical and nanotechnological applications.

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