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ARTICLE

Synthesis of potential bisphenol A substitutes by isomerising metathesis of renewable raw materials

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Isomerising metathesis is introduced as a sustainable method to produce dihydroxystilbene derivatives from eugenol, a clove oil ingredient, and of cardanol from cashew nut shell liquid. Hydrogenation of the dihydroxystilbenes provided their di(hydroxyphenyl)ethane analogues. In initial studies to convert these monomers into polycarbonates and thiol-ene polymers support their potential to replace the petrol-derived bisphenol A (BPA). The estrogenic activity of the monomers derived from cardanol was found to be in the same range as BPA, a known endocrine disruptor. In contrast, the eugenol-derived materials were found to be non-estrogenic, opening up perspectives for bio-based food packaging materials.

Introduction

Polymers are prevalent in everyday life, and their manufacture represents a major sector of the chemical industry.[1] With rising public concern over the rapid depletion of petrochemical resources, efforts to incorporate biomass into the chemical value chain are booming,[2-4] for instance in the field of bio-based polymers.[5-7]

Bisphenol A (BPA) is one of the highest-volume monomers currently produced on about 4.5 million t/a scale (Figure 1).[8] It is the main precursor of polycarbonates and epoxy resins. These polymers present excellent thermal, mechanical, optical and electrical properties.[9-11] They find broad application in end products ranging from construction materials to coatings, thermal paper and electronic equipment all the way to food packaging and containers.[12-14] However, especially for uses in infant feeding bottles, health concerns have been raised on the grounds of the ability of BPA to mimic the hormone estradiol.[15,16] Its ability to coordinate to estrogen receptors arises from the presence of *para*-hydroxy groups with a defined distance.[17,18] BPA exposure has been shown to affect the cardiovascular,[19] reproductive,[20] and immune system[21] as well the neurobehavioral development of children.[22]

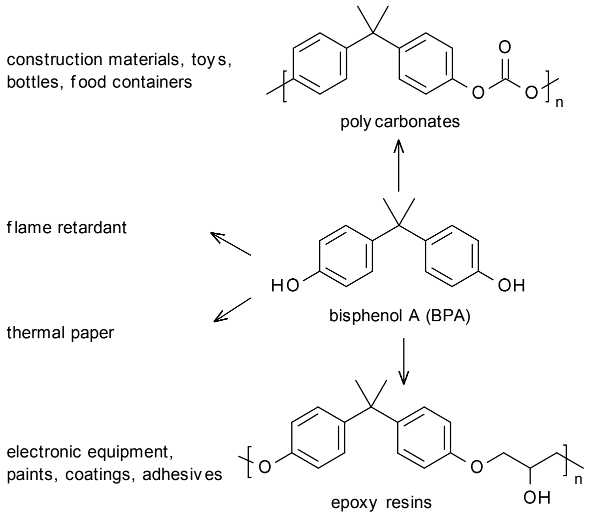

Figure 1 Applications of bisphenol A.

In view of recent US and European legislation banning the use of BPA in the production of polycarbonate infant feeding bottles,[23,24] potential substitutes for BPA for food-related products are highly desirable. For such small-scale applications, health and safety aspects dominate, and sourcing from biomass would constitute a welcome add-on. However, large-volume manufacturing of construction materials would benefit to the greatest degree from the exploitation of renewable raw material sources.

In continuation of our work on the valorisation of bio-based resources by catalytic methods,[25-27] we searched for renewable monomers that would give polymers structurally similar to the BPA-derived materials. Ideally, the target structures would compare favourably with established bisphenol building blocks such as bisphenols A, B, F or S, with regard to estrogenicity.[28,29]

Our plan was to convert naturally occurring alkenyl phenols to the corresponding dihydroxystilbenes *via* isomerising olefin metathesis (Scheme 1).[30-32] We were optimistic that the

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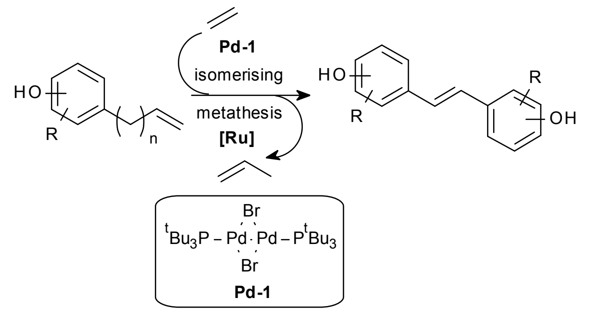


Scheme 1 Synthesis of dihydroxystilbenes from alkenyl phenols.

stilbenes or their hydrogenated di(hydroxyphenyl)ethane analogues would be suitable monomers for the intended application, considering that the utility of the dihydroxystilbene substance class in polymer synthesis has previously been shown.[33-35] The stilbenes can be expected to have greater rigidity[36] and to permit cross-linking,[37] whereas the di(hydroxyphenyl)ethanes would be more flexible, inert building blocks. For this reason, both substance classes appeared to be desirable test materials.

Isomerising metathesis is an orthogonal tandem catalysis process, in which an isomerisation catalyst continuously moves a double bond along a carbon chain, while a metathesis catalyst simultaneously shuffles the substituents at the double bond. A special application is the ethenolysis of alkenyl arenes, which leads to the continuous shortening of the alkenyl side chains with concomitant conversion of ethylene to the valuable propylene. This concept has successfully been applied to the synthesis of styrenes from allylarenes, and of the tsetse-attractant kairomones from cashew nut shell liquid (CNSL).[27] CNSL (Figure 2) would be an ideal starting material also for the present application, because it is a waste product of the cashew nut industry, for which no competition occurs between land use for food or raw material production.[38] Its annual production amounts to about 450,000 tonnes.[39] Crude CNSL consists of a mixture of phenols, terpenes, resorcinols, and salicylic acids bearing C-15 aliphatic side chains with different degrees of unsaturation.[40] Common commercial CNSL is obtained by dry distillation of the nut shells, resulting in decarboxylation of the acids and condensation of a liquid fraction containing mostly cardanols.[41] We have previously demonstrated that this CNSL fraction can be converted into 3-(non-8-enyl)phenol (**1**) in up to 89% yield by ethenolysis followed by distillation.[27] When subjected first to isomerising ethenolysis and then to self-metathesis, we reasoned that **1** would be converted to 3,3'-dihydroxystilbene. The main uncertainty associated with this synthetic approach was the feasibility of the final self-metathesis step, since in previous ethenolysis experiments, no more than traces of the stilbene had been detected as a side product. The self-metathesis of vinyl arenes is also far from trivial, with few known examples of functionalised stilbenes accessed this way.[42-49]

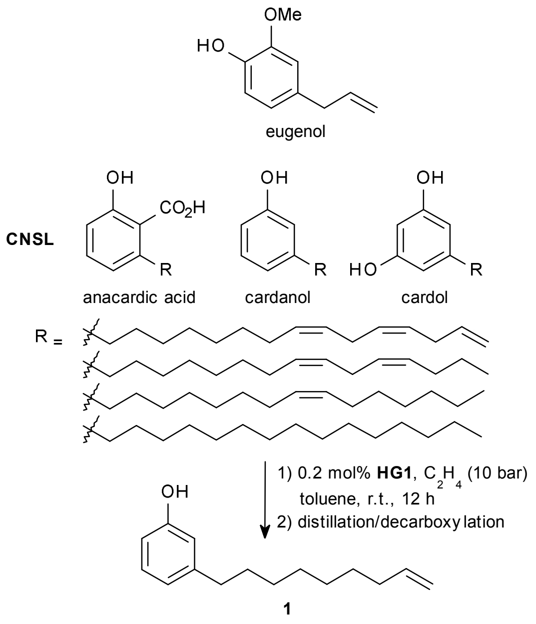
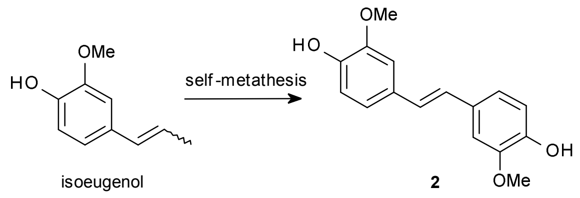


Figure 2 Eugenol and CNSL ingredients.

Another potential raw material is eugenol, an allylarene contained in the essential oils of several plants, such as clove, basil, bay, and tarragon.[50] It has found applications in the pharmaceutical, flavour and fragrance industries.[51,52] Although it may also be synthesised from guaiacol and allyl chloride,[53] eugenol is preferentially isolated from natural sources. About 2000 t/a are produced from clove oil.[54] Starting from eugenol, an isomerising metathesis should directly lead to 3,3'-dimethoxy-4,4'-dihydroxystilbene (**2**). This approach is challenging, because it combines a difficult alkenylarene metathesis with an *in situ* double-bond isomerisation. Bruneau *et al.* have shown that under standard metathesis conditions, the stilbene is formed only as a minor side product.[55] Hitce *et al.* successfully prepared 4,4'-dihydroxy-3,3'-dimethoxystilbene (**2**) from isoeugenol (Scheme 2),[56] of which the preparation requires additional reaction steps.[57,58] It was, however, unclear whether their metathesis catalyst would be compatible with an isomerisation catalyst.

We herein report the preparation of di(hydroxyphenyl) monomers from bio-based starting materials, their conversion into polycarbonates and thiol-ene polymers, and their evaluation with regard to monomer estrogenicity and some basic polymer properties.



Scheme 2 Hitce's synthesis of 4,4'-dihydroxy-3,3'-dimethoxystilbene **2**.

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Experimental

General Methods

All reactions were performed in oven-dried glassware containing a teflon-coated stirring bar. Solvents were purified and dried by standard procedures, and degassed by three freeze-pump-thaw cycles or in case of cyclohexane by argon sparge prior to use prior to use. GC analyses were carried out using a HP6890 with HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25, 100/2.3-30-300/3) and a time program beginning with 2 min at 60 °C, followed by a 30 °C/min ramp to 300 °C, then 3 min at this temperature. Commercial substrates were used as received unless otherwise stated. Cardanol was received from Cardolite and used after purification *via* acidic and basic aqueous work-up. The metathesis catalysts used herein are commercially available, for example from Umicore or Sigma Aldrich. Ethylene was purchased from Air Liquide GmbH (purity 99,95%).

Optimisation of the reaction conditions for the isomerising metathesis of eugenol

Under a nitrogen atmosphere an oven-dried 20 mL vial with a teflon-coated stirring bar was charged with eugenol (156 µL, 1.00 mmol). A stock solution containing **Pd-1** (3.89 mg, 50.0 µmol) and the metathesis catalyst (10.0 µmol) in the given solvent (1 mL) was added via syringe. The resulting mixture was stirred at the given temperature for the given time. After cooling down to r.t., the precipitated product was filtered off, washed with toluene (5 mL) and pentane (2 mL), and dried under reduced pressure. To the combined organic phases *n*-decane (50.0 µL, 258 µmol) was added and a representative sample was filtered through a plug of celite and $MgSO_4$ and analysed by GC / GC-MS.

Preparative scale synthesis of (E)-4,4'-dihydroxy-3,3'-dimethoxystilbene (2) by isomerising metathesis of eugenol

In a glove box, an oven-dried 50 mL vial with a teflon-coated stirring bar was charged with **Pd-1** (23.3 mg, 30.0 µmol) and **M51** (9.83 mg, 15.0 µmol). Eugenol (4.69 mL 30.0 mmol) was added via syringe under nitrogen atmosphere outside the glovebox. The resulting mixture was stirred at 70 °C for 4 h. After cooling to r.t., the precipitated product was filtered off, washed with toluene (3x10 mL) and pentane (3x2 mL) and dried under reduced pressure to yield the desired product as a pale pink solid (3.31 g, 81%). The analytical data obtained matched those reported in the literature.[56] Quantitative GC / GC-MS analysis of the combined organic phases revealed 10% unreacted isoeugenol, 3% of the cross-metathesis by-product between eugenol and isoeugenol (**2a**) and 4% of the eugenol self-metathesis by-product (**2b**).

Synthesis of 4,4'-dihydroxy-3,3'-dimethoxy-diphenylethane (3) starting from (E)-4,4'-dihydroxy-3,3'-dimethoxystilbene (2)

A 50 mL glass reactor was charged with **2** (1.37 g, 5.00 mmol), Pd/C (0.05 mmol) and EtOH (20 mL). The reactor was pressurised with 7 bar H_2 and heated at 50 °C for 5 h. After depressurising, the suspension was filtered through a plug of celite and eluted with EtOH (30 mL). The solvent was removed under reduced pressure to yield **3** as a white solid (1.30 g, 95%).

One-pot synthesis of 4,4'-dihydroxy-3,3'-dimethoxy-diphenylethane (3) starting from eugenol

In a glove box, a 250 mL autoclave equipped with a teflon beaker and a teflon-coated stirring bar was successively charged with **Pd-1** (23.3 mg, 0.03 mmol), **M51** (9.83 mg, 15.0 µmol) and eugenol (4.69 mL 30.0 mmol). The autoclave was stirred at 70 °C for 4 h outside the glovebox. After cooling down to r.t., Pd/C (160 mg, 0.15 mmol) and EtOH (120 mL) were added. The reaction mixture was stirred at 70 °C for 4 h outside the glovebox. After cooling down to r.t., Pd/C (160 mg, 0.15 mmol) and EtOH (120 mL) were added. The autoclave was pressurised with 10 bar H_2 and the reaction mixture was stirred at 50 °C for 5 h. After depressurising, the suspension was filtered through a plug of celite and eluted with EtOH (100 mL). The volatiles were removed under reduced pressure and the resulting solid was washed with a minimum of toluene (3x2 mL) and pentane (3x2 mL) to yield a white solid (3.28 g, 80%). The analytical data obtained matched those reported in the literature.[67]

Optimisation of the reaction conditions for the isomerising metathesis of 3-(non-8-enyl)phenol (1)

In a glove box, a 35 mL oven-dried Ace pressure vessel with a teflon-coated stirring bar was charged with **Pd-1** (5.83 mg, 7.50 µmol) and the metathesis catalyst (10.0 µmol). Subsequently, 3-(non-8-enyl)phenol (109 mg, 0.50 mmol) and the solvent (2 mL) were added. The vessel was pressurised with ethylene outside the glovebox and the mixture was allowed to stir at the given temperature for the given time. After cooling down to r.t., the precipitated product was filtered off, washed with toluene (5 mL) and pentane (2 mL), and dried under reduced pressure. To the combined organic phases *n*-decane (50.0 µL, 258 µmol) was added and a representative sample was filtered throught a plug of celite and $MgSO_4$ and analysed by GC / GC-MS.

Preparative scale synthesis of (*E*)-3,3'-hydroxystilbene (4) by isomerising metathesis of 3-(non-8-enyl)phenol (1)

In a glove box, a 185 mL oven-dried Ace pressure vessel with a teflon-coated stirring bar was charged with **Pd-1** (117 mg, 0.15 mmol) and **M73iPr** (165 mg, 0.20 mmol). Subsequently, 3-(non-8-enyl)phenol (2.18 g, 10.0 mmol) and cyclohexane (40 mL) were added. The vessel was pressurised with 4 bar ethylene (ca. 3 equiv.) outside the glove box and the resulting mixture was stirred at 50 °C for 6 h. The excess ethylene was then removed by flushing the reaction vessel with argon and the reaction was allowed to stir at 50 °C for another 12 h. After cooling down to r.t., the precipitated product was filtered off, washed with toluene (3x5 mL) and pentane (3x2 mL) and dried under reduced pressure to yield the desired product as a gray solid (782 mg, 74%). The analytical data obtained matched those reported in the literature.[59] Quantitative GC / GC-MS analysis of the combined organic phases revealed 21% of the C-2 phenol derivative **5**, 4% of the C-3 phenol derivative **6**.

Synthesis of 3,3'-dihydroxy-diphenylethane (7) starting from (*E*)-3,3'-hydroxystilbene (4)

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A 50 mL glass reactor was charged with **4** (1.06 g, 5.00 mmol), Pd/C (0.05 mmol) and EtOH (20 mL). The reactor was pressurised with 7 bar H_2 and heated at 50 °C for 5 h. After depressurising, the suspension was filtered through a pad of celite and eluted with EtOH (30 mL). The solvent was removed under reduced pressure to yield **7** as a white solid (1.01 g, 99%).

One-pot synthesis of 3,3'-dihydroxy-diphenylethane (7) starting from 3-(non-8-enyl)phenol (1)

In a glove box, a 185 mL oven-dried Ace pressure vessel with a teflon-coated stirring bar was charged with **Pd-1** (117 mg, 0.15 mmol) and **M73iPr** (165 mg, 0.20 mmol). Subsequently, 3-(non-8-enyl)phenol (2.18 g, 10.0 mmol) and cyclohexane (40 mL) were added. The vessel was pressurised with 4 bar ethylene (ca. 3 equiv.) outside the glove box and the resulting mixture was stirred at 50 °C for 6 h. The excess ethylene was then removed by flushing the reaction vessel with argon and the reaction was allowed to stir at 50 °C for another 12 h. After cooling down to r.t., a solution of activated charcoal (1.20 mg, 0.10 mmol) in EtOH (40 mL) was added. The vessel was pressurised with 7 bar hydrogen and stirred at 50 °C for 5 h. After depressurising, the suspension was filtered through a plug of celite and eluted with EtOH (50 mL). The volatiles were removed under reduced pressure and the resulting solid was washed with a minimum of toluene (3x2 mL) and pentane (3x2 mL) to yield the desired product as a white solid (770 mg, 72%). The analytical data obtained matched those reported in the literature.[60]

General procedure for the synthesis of polycarbonates

A 30 mL radley carousel tube was charged with bisphenol (1 equiv.), diphenyl carbonate (193 mg, 900 µmol, 1 equiv.) and lithium hydroxide (1.10 mg, 46.0 µmol, 5 mol%) under argon atmosphere. The resulting mixture was heated at 180 °C for 24 h. The reaction was quenched by cooling to r.t. and addition of THF (3 mL). The polymer was precipitated in cold methanol (30 mL), filtered and dried over phosphorous pentoxide at 10^{-3} mbar for 24 h.

General procedure for the synthesis of thiol-ene polymers

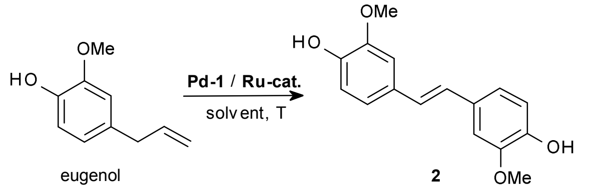
A 10 mL Ace pressure vessel was charged with diallyl (1 equiv.) and decane dithiol (146 mg, 707 µmol, 1 equiv.) under argon atmosphere. After stirring at 50 °C for 10 min, AIBN (2.8 mg, 17.0 µmol, 2.5 mol%) was added and the resulting mixture was heated at 75 °C for 5 h. The mixture was then dissolved in THF (2 mL) and the polymer was precipitated in cold methanol (30 mL), filtered and dried over phosphorous pentoxide at 10^{-3} mbar for 24 h.

Results and discussion

Synthesis of di(hydroxyphenyl) derivatives from eugenol

As a starting point, the isomerising metathesis of eugenol was investigated using a combination of 0.5 mol% isomerisation catalyst $[Pd(\mu\text{-Br})(^{t}Bu_3P)]_2$ (**Pd-1**)[61-64] and 0.1 mol% metathesis catalyst **M51** in THF at 50 °C while applying the conditions previously described in a related isomerising ethenolysis (Table 1, see also Table S1 in the SI).[27] Since no metathesis product was formed (entry 1), we systematically screened various solvents and found toluene to be uniquely effective. This was unexpected, because dichloromethane and THF generally perform better in olefin metatheses (entries 2, 3 and 4).[65,66]

Table 1 Isomerising metathesis of eugenol[a]



Entry	Ru-cat. / (mol%)	T (°C)	Solvent	**2** (%)
1	**M51** (0.1)	50	THF	n.d.
2	"	"	DCM	n.d.
3	"	"	cyclohexane	62
4	"	"	toluene	82
5	**G2** (0.1)	"	"	67
6	**M31** (0.1)	"	"	31
7	**M42** (0.1)	"	"	n.d.
8	**M73** (0.1)	"	"	79
9	**M93** (0.1)	"	"	80
10	**M51** (0.1)	r.t.	"	63
11	"	60	"	85
12	"	70	"	91
13	"	80	"	88
14[b]	**M51** (0.05)	70	"	84
15[b, c]	"	"	"	93
16[b, c, d]	"	"	none	81

[a] Reaction conditions: eugenol (1 mmol), **Ru-cat.** (0.1 mol%), **Pd-1** (0.5 mol%), solvent (1 mL), 1 h, isolated yields; [b] **Pd-1** (0.1 mol%); [c] 4 h; [d] 30 mmol scale.

The screening of various ruthenium-based metathesis catalysts (Figure 3) revealed that the modified Hoveyda-Grubbs catalyst **M51** performed best (entries 5-9). The yields could be improved further by raising the temperature, with optimum catalyst performance at 70 °C (entries 10-13). Even at catalyst loadings as low as 0.05 mol% **M51** and 0.1 mol% **Pd-1**, near-quantitative yields were obtained if the reaction time was increased from 1 h to 4 h (entries 14 and 15). Under these optimal conditions, the reaction proceeded highly selectively. The pure product **2** precipitated in 93% yield and was isolated by filtration. Analysis of the filtrate by GC / GC-MS showed 3% yield of isoeugenol, but no eugenol self- or cross-metathesis side products. By performing the reaction under more sustainable bulk conditions, we were able to scale up the reaction and provide sufficient material for polymerisation tests (entry 16). In the absence of solvent, **2** was isolated in 81% yield, but the amount of undesired side products increased to 4 % of eugenol self-metathesis products and 3% of cross-metathesis products between eugenol and isoeugenol. A substantial decrease in the *E*-factor (total kg waste per kg product) from 7.1 to 0.5 was achieved.

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The stilbene double bond was then hydrogenated using 1 mol% Pd/C either starting from isolated **2**, or by adding the palladium catalyst to the crude reaction mixture and stirring it for another 5 h at 50 °C with 10 bar hydrogen pressure. The one-step procedure afforded 80% overall yield of the di(hydroxyphenyl)ethane **3** (Scheme 3). When using the metals already present in the solution as hydrogenation catalysts, the conversion of the one-pot procedure was high but not quantitative.

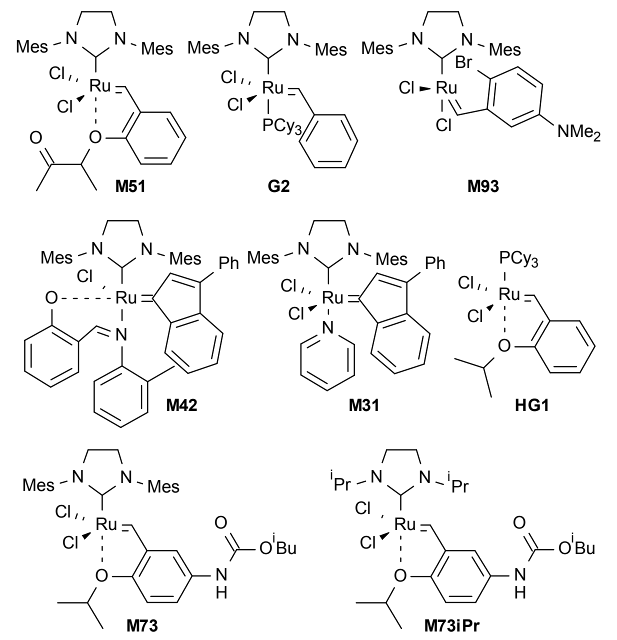
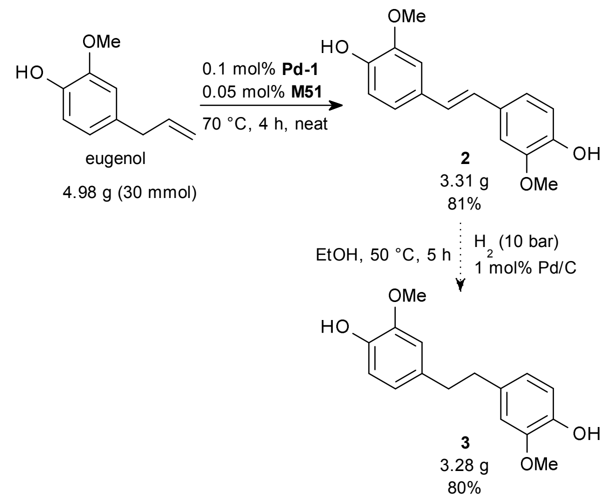


Figure 3 Metathesis catalysts.



Scheme 3 Synthesis of di(hydroxyphenyl) derivatives from eugenol *via* isomerising metathesis and optional hydrogenation.

Synthesis of di(hydroxyphenyl) derivatives from CNSL

Cashew nut shell liquid is commercially available in various qualities. The higher the thermal stress applied in its manufacture, the lower is the content of anacardic acids (see Figure 2). Ideally, any of these mixtures should directly be converted into 3,3'-dihydroxystilbene (**4**) when first subjected to isomerising metathesis in the presence of ethylene with constant removal of volatile olefins, and then to high-temperature distillation with concomitant decarboxylation. However, present isomerisation catalysts are incompatible with the polyene components present in crude cardanol. For this reason, an additional ethenolysis step is required upfront. We thus first treated a commercial CNSL containing mostly phenols with saturated, mono- and polyunsaturated side chains with 10 bar ethylene in toluene in the presence of 0.2 mol% **HG1** (Figure 2). Fractional distillation caused any anacardic acids to decarboxylate, so that 3-(non-8-enyl)phenol (**1**) was isolated in 84% yield as the distillate, whereas resorcinols and saturated C-15 phenols formed the distillation residue and volatile olefins evaporated.

The next step towards dihydroxystilbene **4** was the development of a tandem isomerising ethenolysis / homo-metathesis process. First, isomerising ethenolysis would continually shorten the nonenyl chains of **1** with release of volatile short-chain olefins. The resulting 3-vinylphenol intermediate would then undergo self-metathesis with release of ethylene to form the desired product. Because most catalysts would preferentially mediate the metathesis between two substrates with longer alkenyl chains, the key challenge was to maximise ethylene intake. At the same time, the catalyst would have to be capable of a self-metathesis of vinylarenes, which have a particularly low reactivity.

We started our search for a suitable catalyst system with conditions developed for the synthesis of vinylarenes from cardanol,[27] involving 1.5 mol% of isomerisation catalyst **Pd-1** and 2 mol% of metathesis catalyst **M51** (Table 2, see also Table S2 in the SI). In THF, C-2 and C-3 phenol derivatives **5** and **6** were formed as major products, indicating a too-high preference for ethenolysis (entry 1). In other common metathesis solvents, mixtures of longer-chain alkenyl phenols were obtained (R>CH_3), indicating that the reaction rate is rather slow (entries 2-4). Systematic evaluation of ruthenium-based metathesis catalysts in cyclohexane revealed the unique selectivity profile of **M73iPr** (entry 5), which was the only one to give the desired product in reasonable yield. The yield of **4** was further improved by fine-tuning the reaction conditions, i.e. adjusting the ethylene pressure to 1 bar (ca. 3 equiv.), investigating the optimal reaction temperature, and removing excess ethylene by argon exchange after 6 h and continuing to stir overnight (entries 8, 9, 10). Under the optimal conditions (entry 10), **4** precipitates and was isolated in pure form in 79% yield simply by washing the precipitate with toluene and pentane. The combined filtrates contained a further 5% yield of product **4**, along with 12% yield of side products **5** and **6**, along with traces of longer-chain alkenyl arenes (R>CH_3).

When ethylene was left out altogether, the product was still obtained in 30% yield, which may be explained with a preference of the catalyst for vinylarene homo-metathesis or the exceptionally low energy of formation of the stilbene product (entry 11), since the equilibrium content of the

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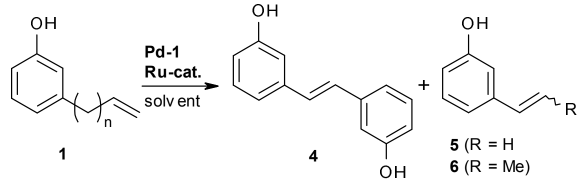
conjugated alkenylphenol is 35% rather than the 60% required for this reaction outcome purely by statistics.

Table 2 Isomerising metathesis of 3-(non-8-enyl)phenol (1)[a]

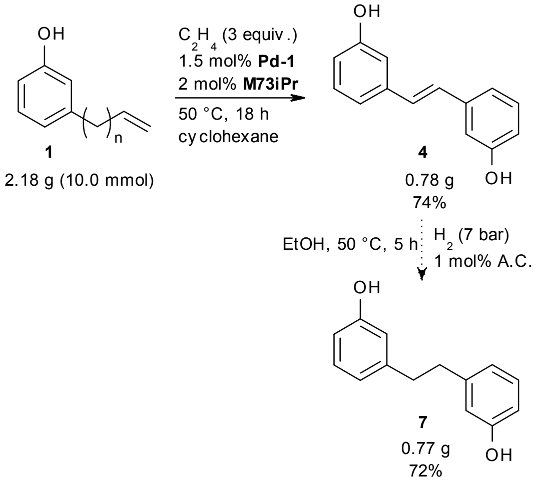


Entry	Solvent	**Ru-cat.**	**4** (%)	**5 + 6** (%)[b]	R > CH_3 (%)[b]
1	THF	**M51**	n.d.	93	traces
2	DCM	"	n.d.	23	76
3	toluene	"	n.d.	8	90
4	cyclohexane	"	n.d.	n.d.	99
5	"	**M73iPr**	68	18	traces
6	"	**M73**	n.d.	36	64
7	"	**M93**	n.d.	n.d.	99
8[c]	"	**M73iPr**	72	14	traces
9[c, d]	"	"	69	15	traces
10[c, e]	"	"	79	12	traces
11[f]	"	"	30	traces	60

[a] Reaction conditions: **1** (0.5 mmol), **Pd-1** (1.5 mol%), **Ru-cat.** (2 mol%), C_2H_4 (6 bar), solvent (2 mL), 50 °C, 18 h, isolated yields; [b] yields were determined by GC using *n*-decane as internal standard; [c] C_2H_4 (1 bar); [d] 70 °C; [e] C_2H_4-argon exchange after 6 h; [f] without C_2H_4.

We were pleased to see that the results were comparable on preparative scale (Scheme 4). The low solubility of the stilbene in non-polar solvents allows isolating the product simply by filtration of the reaction mixture and washing the precipitate with toluene.

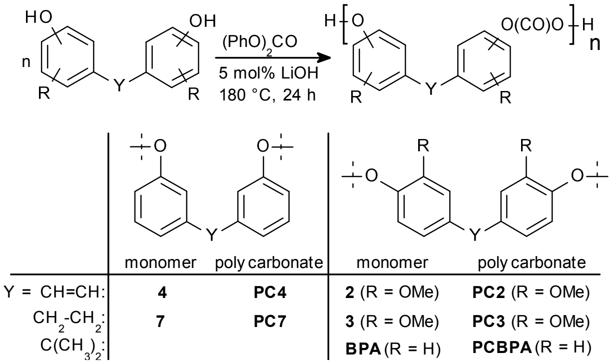
The one-pot procedure can be extended further to include hydrogenation of **4** to the di(hydroxyphenyl) ethane **7**. A ruthenium-on-charcoal hydrogenation catalyst was generated in situ from **M73iPr** by adding ethanol, 1 mol% activated charcoal, and pressurising with 7 bar hydrogen. After 5 hours at 50 °C, **4** was quantitatively converted to **7**.



Scheme 4 Synthesis of di(hydroxyphenyl) derivatives from 3-(non-8-enyl)phenol *via* isomerising metathesis and optional hydrogenation. A.C. = activated charcoal.

Polymerisation studies

Polycarbonates. The first chosen application for the stilbene-based monomers was as polycarbonates (PCs), a typical end product of BPA. Thus, polycarbonates **PC2**, **PC3**, **PC4**, and **PC7** were prepared in a sustainable fashion from the diphenols **2**, **3**, **4** and **7** with diphenyl carbonate and catalytic LiOH at 180 °C, rather than using the conventional phosgene process (Scheme 5). As a reference material, a polycarbonate **PCBPA** was prepared from BPA by the same process.



	monomer	poly carbonate	monomer	poly carbonate
Y = CH=CH:	4	PC4	2 (R = OMe)	PC2 (R = OMe)
CH_2-CH_2:	7	PC7	3 (R = OMe)	PC3 (R = OMe)
$C(CH_3)_2$:			BPA (R = H)	PCBPA (R = H)

Scheme 5 Polycarbonate synthesis.

Table 3 summarises the properties of the polycarbonates obtained from stilbenes **2** and **4**, dihydrostilbenes **3** and **7**, and from BPA.

The eugenol-derived monomers **2** and **3** and the CNSL-derived monomer **7** gave polycarbonates with comparable but rather low average molecular weight (M_n) after 24 hours reaction time. Under the same conditions, BPA led to THF-insoluble polymer **PCBPA1**. In order to allow a comparison with the bio-based polycarbonates, the reaction time for BPA was reduced to 3 hours, affording **PCBPA2** with a M_n in the desired range. The CNSL-derived monomer **4** led to THF-insoluble polymer already after 40 min, so that no M_n could be measured. The dispersity ($Đ$) values for the soluble polymers **PC2**, **PC3**, **PC7**, and **PCBPA2** vary between 1.5 and 2.0, as can be expected for a step-growth polymerisation. Thus, the M_n as well as dispersities of the PCs from renewables, both comparable to **PCBPA2**, demonstrate that these monomers are reactive in polycarbonate synthesis.

Thermal properties, such as melting points and glass transition temperature, depend on the chemical structure of the polymer as well as on M_n. Thus, only polymers with similar M_n can be compared, especially for rather low-molecular-weight materials as obtained here. The melting points of polycarbonates **PC2**, **PC3**, and **PC7** were below 150 °C, whereas the BPA-based polymer **PCBPA2** with similar M_n melted at 224-228 °C, a difference attributable to structural factors.

The glass transition temperature (T_g) ranges from 25 °C for **PC7** to 127 °C for **PC2** for the polymers with M_n of 2000-3500.

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Polymer **PC3** showed a T_g of 81 °C, in agreement with literature reports.[67] This temperature is comparable to that of **PCBPA2** at similar molecular weights, indicating a similar rigidity of the two polymers. Hydrogenation of the stilbene increases the flexibility of the chain reflected by a decrease in T_g of polymers **PC3** and **PC7** compared to their unsaturated equivalents **PC2** and **PC4**. Steric hindrance in the proximity of the hydroxyl group could be a reason why eugenol-derived polymer **PC3** presents higher T_g than its CNSE equivalent **PC7**. A decrease in the melting points from the unsaturated polymer **PC2** to more flexible polymer **PC3** was also observed. For **PC4** and **PC7**, the melting points are hard to interpret due to differences in the M_n. All polymers showed semicrystalline behaviour, which is typical for PCs precipitated from methanol.[68]

Table 3 Summary of the analytical results of polycarbonates[a]

Polymer	M_n (g/mol)	$Đ$	mp (°C)	T_g (°C)	$T_{d\,5\%}$ (°C)
PC2	2800	2.0	146 – 148	127	305
PC4	-[b]	-[b]	258 – 262	160	313
PC3	3500	1.5	106 – 108	81	319
PC7	2200	1.6	143 – 146	25	292
PCBPA1	-[b]	-[b]	280 – 290	115	332
PCBPA2[c]	2700	1.3	224 – 228	79	314

[a] Reaction conditions: bisphenol monomer (1 equiv.), diphenyl carbonate (1 equiv.), LiOH (5 mol%), 180 °C, 24 h; [b] insoluble in THF; [c] 3 h reaction time; properties of materials precipitated from methanol, see SI for details.

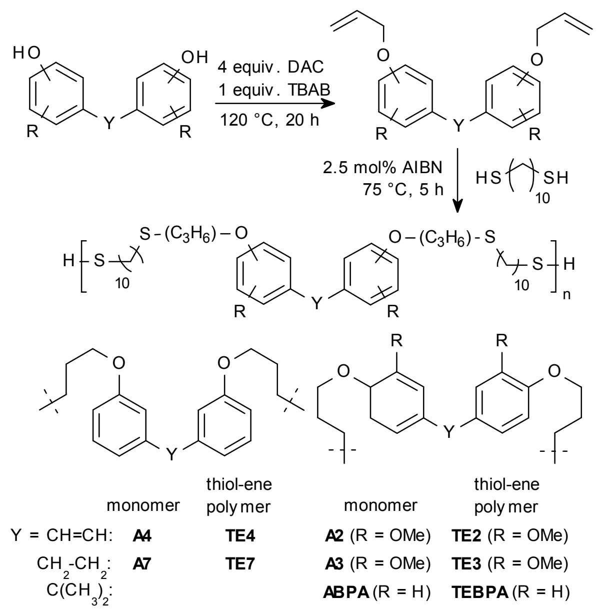
All polymers present excellent degradation temperatures ($T_{d\,5\%}$). For materials with a similar molecular weight range, $T_{d\,5\%}$ for **PC3** (319 °C) is closest to that of the BPA-based polymer **PCBPA2** (314 °C). **PC2** and **PC7** have slightly lower degradation temperatures, but the values for all polycarbonates are within a narrow range between 292 and 332 °C.

Overall, polymers with a wide range of thermal properties were obtained. The reactivity of the monomers and characteristics of the polymers are promising in terms of a possible substitution of bisphenol A, but intensive future research will be required to ultimately prove this.

Thiol-ene polymerisation. To complement our studies, we investigated the reactivity of our di(hydroxyphenyl) derivatives in a different polymer class. We chose thiol-ene addition, which is an efficient, sustainable polymerisation technique performed under mild conditions.[69,70]

The first step was the allylation of the phenols to afford diallyl derivatives. The procedure can be carried out either *via* conventional Williamson reaction or *via* a more sustainable route using diallyl carbonate instead of the toxic allyl bromide (Scheme 6).[71] Both pathways afforded the allylated monomers **A2**, **A4**, **A3**, **A7** and **ABPA** in good-to-excellent yields (see SI).

The thiol-ene polymerisation was carried out using the allylated monomer and one equivalent of decane dithiol, using AIBN as radical initiator, as shown in Scheme 6. The properties of the thiol-ene polymers and the analogous BPA-based reference polymer **TEBPA** are summarised in Table 4.



Scheme 6 Thiol-ene polymerisation. DAC = diallyl carbonate.

Table 4 Summary of the analytical results of thiol-ene polymers[a]

Polymer	mp (°C)	M_n [g/mol]	$Đ$	$T_{d\,5\%}$ [°C]
TE2[b]	25 – 50	2700	1.7	301
TE4	25 – 50	3100	7.1	316
TE3	25 – 50	4300	3.0	336
TE7	25 – 50	16600	5.3	311
TEBPA	r.t.	5200	3.6	270

[a] Reaction conditions: diallyl monomer (1 equiv.), decane dithiol (1 equiv.), AIBN (2.5 mol%), 75 °C, 5 h. [b] in THF; properties of material precipitated from methanol, see SI for details.

Polymer **TE3** showed similar M_n and $Đ$ values to **TEBPA**, but the best reactivity (highest M_n) was observed for CNSE-derived monomer **7** to form polymer **TE7** with a molecular weight of 16000 g/mol. The liquid mixture became viscous already after 30 min. reaction time. The broad dispersity value ($Đ$ = 5.3) of polymer **TE4**, as well as a broadening of the ^{1}H NMR peaks (see SI), indicate that cross-linking took place. The same phenomenon was observed for polymer **TE2**, but with a lower reactivity, which may be explained by the increased steric hindrance of the ortho-methoxy group in **2**. The allylated CNSE derivative **A4** is liquid at room temperature, whereas the eugenol counterpart **A2** has a melting point of 141 °C, making the reaction in bulk impossible. For the polymerisation of **A2**, additional solvent was required and consequently, the lower concentration could have also decreased the molecular weight obtained. The thermal properties were similar for all thiol-ene polymers, with degradation temperatures ranging from 270 °C in the case of **TEBPA** to 336 °C for **TE3**.

The results obtained in the thiol-ene polymerisation point to another potential application of these monomers derived from renewable resources. The saturated monomers are suitable for linear polymers, whereas cross-linking in the stilbene-based monomers allows their use in resin synthesis.[72] Comparing

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these results to those for PCs described above, a wide range of properties may be achieved. Unsurprisingly, the thiol-ene polymers were obtained in higher molecular weights due to better solubility during polymerisation as well as less steric hindrance of the monomers employed. These preliminary investigations suggest that the polymers prepared starting from renewable resources have promising properties, but further investigations are clearly required to assess the mechanical properties of the bulk materials.

Estrogenicity assay

For potential applications in food packaging, degradation of the polymers with release of estrogenic monomers is a major concern. To assess the estrogenicity of the di(hydroxyphenyl) building blocks **2**, **4**, **3**, and **7**, we subjected them to a yeast estrogen screen (YES).[73] YES is a reporter gene assay that measures human estrogen receptor alpha (hERα) activation. The yeast cell nucleus is genetically modified to contain the gene for the human estrogen receptor along with a vector composed of a promoter region and lacZ gene. The estrogen receptor is expressed by the yeast cell and attaches to the estrogen receptor elements (ERE) within the promoter. Binding of an estrogenic substrate to the receptor switches on the promoter, leading to expression of the lacZ gene and production of β-galactosidase. This enzyme is released into the medium, where it converts added chlorophenol red-β-D-galactopyranoside (CPRG) to chlorophenol red (CPR). The colour change from yellow to red is quantified photometrically.

Figure 4 shows the concentration-response curves for hERα activation by our test compounds along with a BPA calibration curve. The measurements were run at concentrations ranging from 11 to 750 µg/L. At 750 µg/L BPA, the receptor activation equals that of estradiol at a concentration of 0.05 µg/L.

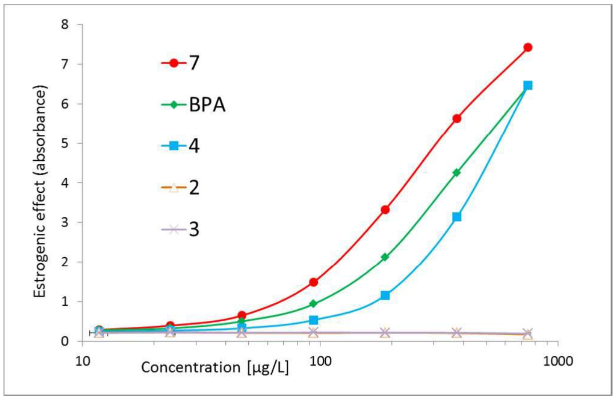

Figure 4 Yeast estrogen screen.

The estrogenicities of the cardanol-derived compounds **4** and **7** were found to be similar to BPA. Thus, changing the position of the hydroxy groups from para to meta did not advantageously affect this outcome. This is remarkable because the endocrine disrupting ability of 3,3'-dihydroxy-diphenylmethanes was previously shown to be lower than that of BPA.[16] In contrast, we were pleased to find that the eugenol-derived monomers **2** and **3** showed considerably lower estrogenicity.[74] The lower estrogen receptor affinity caused by the *ortho*-methoxy groups may be attributed to steric hindrance. This is in line with observations made for the *ortho*-methoxy-substituted BPA analogue 2,2-bis(4-hydroxy-3-methoxyphenyl)propane, which was found not to displace estradiol in a competitive binding assay.[75]

Conclusions

Overall, it was demonstrated that isomerising metathesis is a viable concept for the sustainable synthesis of di(hydroxyphenyl) derivatives starting from renewable resources including eugenol and cardanol. The estrogenic activity of the monomers derived from cardanol was found to be in the same range as BPA, whereas the eugenol-derived materials were found to be non-estrogenic. Polycarbonate and thiol-ene polymers were prepared from the dihydroxystilbene and dihydroxy-dihydrostilbene monomers, demonstrating their general usefulness. Future studies need to address mechanical as well as other material properties of these novel polymers in order to ascertain the viability of the present strategy to replace bisphenol A with sustainable alternatives. The lack of estrogenic activity in the eugenol-derived monomers makes them suitable candidates for the development of novel bio-based food packaging materials, while the polymers derived from cashew nut shell liquid may become a welcome alternative to petrol-derived BPA materials in non-food applications.

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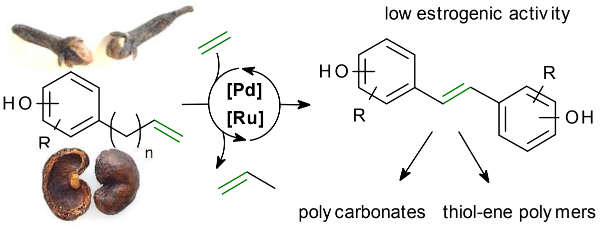
Plant-derived alkenyl arenes were converted to polymer building blocks with low estrogenic activity *via* isomerising metathesis.



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