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Structure-Performance Guided Design of Sustainable Plasticizers from Biorenewable Feedstocks

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The search for more sustainable solutions for plastics production, moving away from petrochemical feedstocks as today's major raw material basis, is a research area of increasing interest. This task goes far beyond the issue of designing greener polymers and their related monomers as tailor-made plastics require, besides the polymer itself, further components. These additives also need to be switched from typically fossil-based to bio-renewable raw materials. One of such necessary components for many applications are plasticizers, and a major application of them is related to polyvinyl chloride (PVC) as one of the leading polymers with a wide range of applications. Typically today's plasticizers are based on fossil feedstocks, and some of them such as specific ortho-phthalates as the most important product class of plasticizers are now subject to restrictions and authorization by the EU's REACH legislation due to their toxicological profile. In this contribution, we report the synthesis and technical evaluation of alternative, novel bicyclic plasticizer candidates, which are fully accessible from renewable feedstocks. In detail, these new plasticizer target molecules are based on the use of the furan-derivative 2-methylfuran, maleic anhydride and 2-ethylhexanol as bio-based starting materials. The synthetic concept consists of an initial Diels-Alder reaction with 2-methylfuran and a subsequent hydrogenation and optional esterification step. The applied reactions are well-known as economic and sustainable technologies. Thus, not only the starting materials (being of bio-based origin) but also the selected reaction technologies for the syntheses of the target molecules are sustainable. Furthermore, a range of performance tests enabled an insight into structure-performance relationships and revealed promising plasticizing properties of this new bio-based plasticizer generation with, e.g., an attractive solution temperature fulfilling the criterium for a "fast fuser" as well as good compatibility with PVC.

Introduction

Although plastics are currently controversially discussed for pollution issues, the use of polymers is still inevitable for numerous applications, e.g., in the construction and automotive industry or as vital disposables for medical use.[1] They are often superior compared to common materials like wood, metal or glass due to their combination of low cost, low weight and durability as well as, at least in part, sustainability.[2] At the same time, the search for more sustainable solutions moving away from petrochemical feedstocks as the major raw material basis for today's plastics is ongoing. However, when addressing the challenge of sustainable plastics production, this task (and vision as graphically outlined in Figure 1) goes far beyond the issue of designing greener polymers and their related monomers. Today, tailor-made plastics require, besides the polymer itself, further components. These additives also need to be switched from typically fossil-based to bio-renewable raw materials. One of such necessary components for many applications are plasticizers, and a major application of them is related to polyvinyl chloride (PVC) as one of the leading polymers in the European polymer market.[3] After the polyolefins polyethylene (PE) and polypropylene (PP), PVC is accounted for the third-largest share of European production volume of plastics in 2018.[3a] PVC has a wide range of applications as its properties can be modified by additives.[4] Furthermore, very recently an industrial scale production of PVC being fully based on a renewable feedstock has been realized, thus addressing an important sustainability issue in this field of plastics.[3b] For their use in PVC, plasticizers represent the most important category of additives by weight.[5]

Traditionally, ortho-phthalates have represented the most important and well-known product class of plasticizers. However, some of these molecules are now subject to restrictions and authorization by the EU's REACH legislation (Regulation (EC) No. 1907/2006) due to their toxicological profile, and by now have mostly been replaced.[6] For so-called low molecular weight phthalates (LMW) like di(2-ethylhexyl) phthalate (DEHP), reproductive toxicity with presumed endocrine-disrupting activ-

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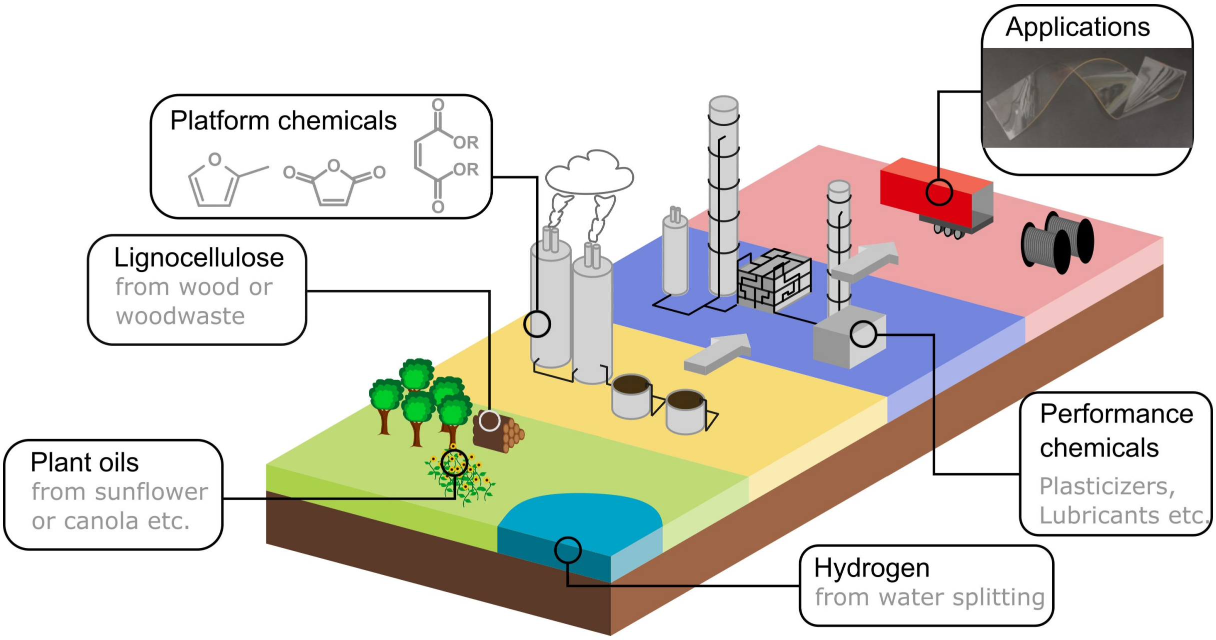


Figure 1. Graphic of the production steps for renewable products such as plasticizers.

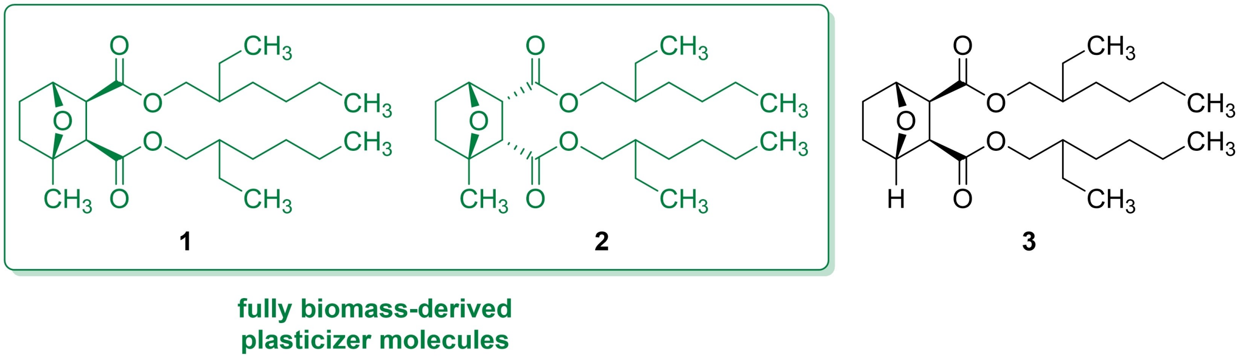
ity was shown.[7] These LMWs are restricted in all articles not explicitly exempted in Annex XVII, entry 51 of REACH (Regulation (EC) No. 1907/2006). With the market launch of dioctyl terephthalate (DEHT) and diisononyl 1,2-cyclohexane dicarboxylate Hexamoll® DINCH, two alternative plasticizers are now available that can be regarded as suitable alternatives and due to their eco-/toxicological profiles, they are used in critical applications such as toys as well as medical and food contact applications.[8,9]

However, up to now these plasticizers used on bulk scale are based, at least to the most extent, on fossil feedstocks. With the goal to find more sustainable products based on biorenewable raw materials, much effort has been made in recent years to develop such bio-based alternatives.[10] As raw materials, citric acid[11] as well as soybean oil,[12] castor oil[13] or cardanol[14] play an important role. Another possible feedstock is based on platform chemicals from bio-renewable resources like lignocellulose for either the synthesis of known compounds or the design of new candidates.[15] Further prominent building blocks are furfural and 5-hydroxymethylfurfural (5-HMF) as well as derivatives thereof.[16] For example, the esters of furan dicarboxylic acids showed good compatibility with PVC and low cytotoxicity. However, bad low-temperature properties and higher volatility compared to DEHP hamper their technical application.[17] Furthermore, the synthesis of 1,2-cyclohexane dicarboxylates and derivatives starting from bio-based fumarates by means of an one-pot cycloaddition of isoprene and hydrogenation was reported.[18] Complementing these efforts, we recently could show the suitability of a 3-methyl-substituted DEHP derivative, which is available from bio-based feedstocks, as a plasticizer.[19] In spite of promising performance properties such as the solution temperature in the PVC test, a drawback of this type of bio-based plasticizer is its too high viscosity.

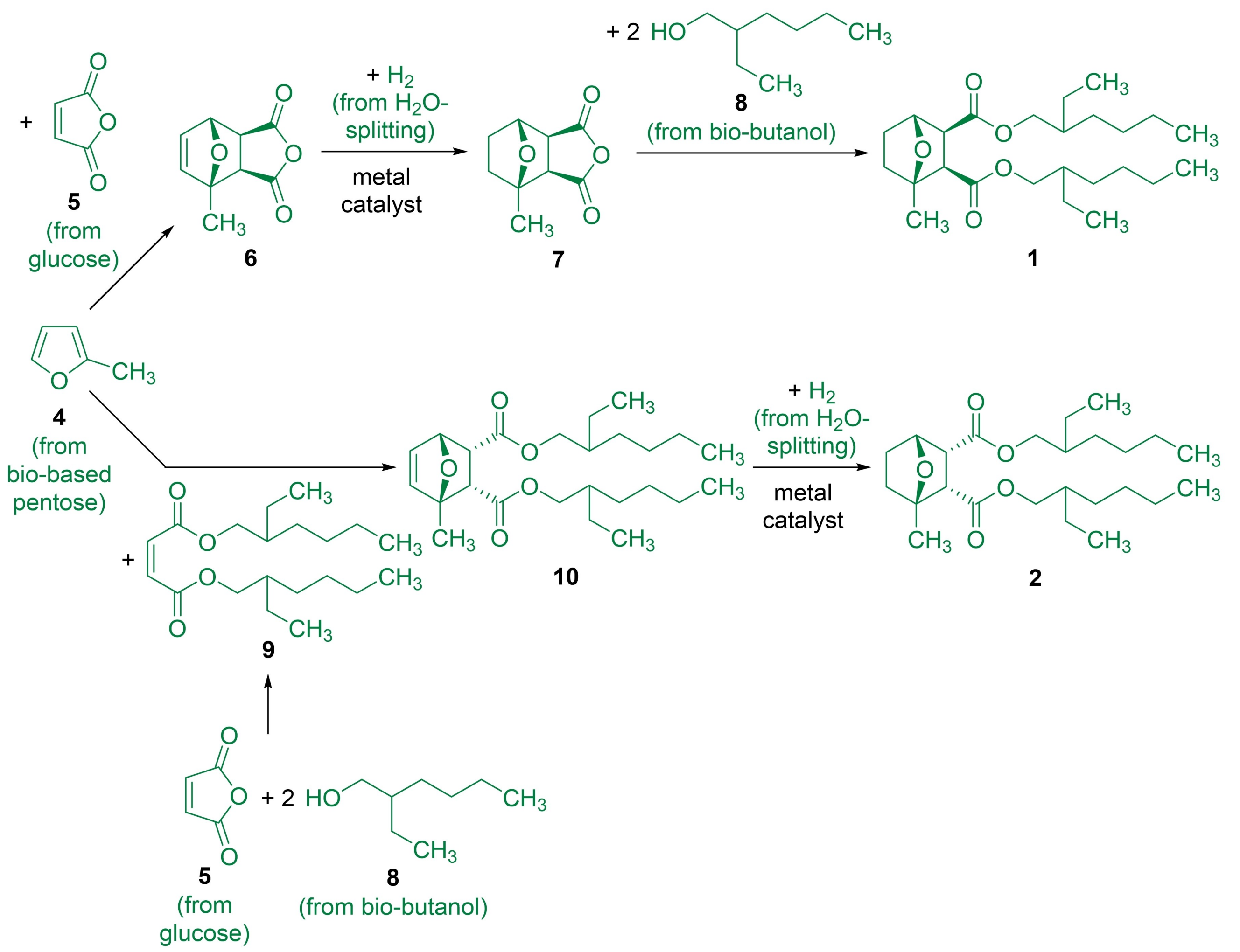
Thus, in spite of all these efforts and the strong demand, a novel generation of plasticizers fulfilling the criteria of a biorenewable feedstock basis, reduced toxicity, unchanged excellent performance features and favored economic access (which certainly is a strong advantage of the current fossil-based plasticizer product portfolio besides excellent performance data) has not been developed yet.

Addressing this challenge of such a bio-based novel plasticizers generation, in this work we present the synthesis and technical evaluation of novel bicyclic plasticizer candidates **1** and **2**, which are fully accessible from renewable feedstocks (Scheme 1). The comparison of the performance tests also enables an insight into structure-performance relationships. In this performance test study, we also included the non-biomass derived, non-methyl-substituted heterocyclic compound **3** for comparison.

he synthetic concept for the first bio-based plasticizer target molecule **1** is based on the use of the furan-derivative 2-methylfuran, maleic anhydride and 2-ethylhexanol as starting materials. It is noteworthy that all these involved starting materials and the reagent, in detail 2-methylfuran, maleic anhydride, molecular hydrogen and 2-ethylhexanol (resulting from bio-based *n*-butanol being currently planned for production on pilot plant scale)[20] can be prepared from renewable feedstocks. As will be outlined more in detail below (Scheme 2), the total (three-step) synthesis of **1** consists of an initial Diels-Alder reaction of 2-methylfuran with maleic anhydride, followed by hydrogenation and esterification with 2-ethylhexanol (Scheme 2). These three individual reactions are in general well-known as economic and sustainable technologies. Thus, not



Scheme 1. Bio-derived plasticizer candidates synthesized and investigated in this study (in case of the racemates **1** and **2**, only one enantiomeric form of the heterocyclic diester substructure is graphically shown).



Scheme 2. Synthetic concepts for the design of new plasticizers from biorenewables (in case of the racemates **1**, **2**, **6**, **7** and **10**, only one enantiomeric form of the heterocyclic diester substructure is graphically shown).

only the starting materials (being of bio-based origin) but also the selected reaction technologies for the syntheses of the target molecules are sustainable.

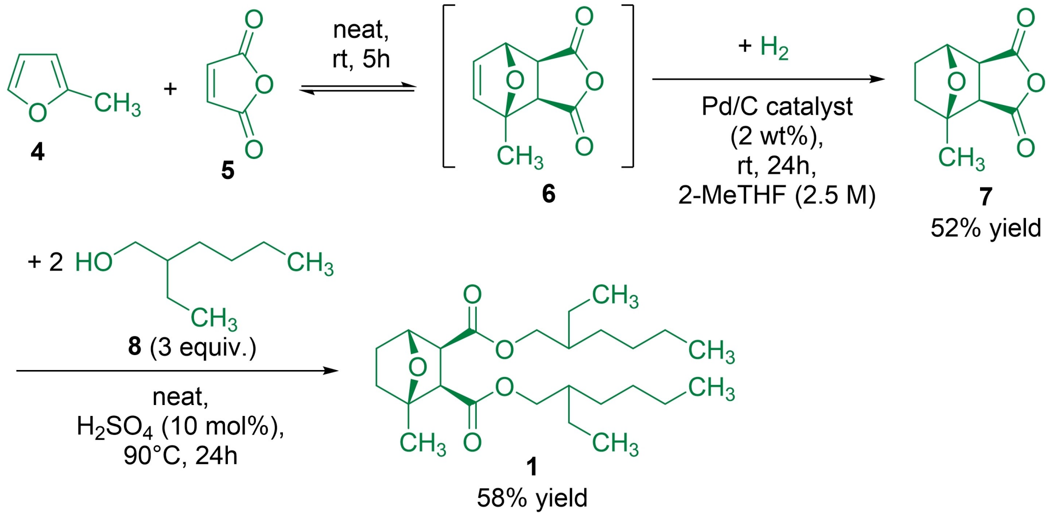
When carrying out the Diels-Alder reaction of 2-methylfuran with *bis*(2-ethylhexyl) maleate instead of maleic anhydride, subsequent hydrogenation then leads to the second plasticizer molecule **2** showing an opposite diastereopreference compared to **1**. The availability of both diastereomers enables a deeper insight into the structure-activity relationship. Besides the bio-based 2-ethylhexyl diesters **1** and **2**, we also included the related non-bio-based and non-methyl-substituted diester **3** in our study, which should provide information about the effect of the methyl-substituent in the target molecules **1** and **2** on their plasticizer performance based on criteria such as, e.g., solution temperature and viscosity data as well as compatibility with PVC. For all the synthesized diester compounds **1**-**3** in our study, a *bis*(2-ethylhexyl) ester subunit was chosen as structural diester motiffor reasons of comparability when investigating the effect of the bicyclic subunit. We will demonstrate that the new bio-based bicyclic diester molecules open up the perspective towards new lead structures of bio-based plasticizers that go beyond "just representing" replacements of the state-of-the-art commercial plasticizer compounds.

Results and Discussion

The synthetic pathways to both bio-based diastereomers **1** and **2** are fully based on the utilization of biorenewable raw materials, and all the reactions leading to **1** and **2** starting from such biorenewable sources are shown in Scheme 2.

As a starting material, bio-based furfural is one of the top 30 biomass-derived platform chemicals, which is annually produced today with more than 200,000 tons. Bio-based materials already serve as the main source of this production of furfural, which is readily available from natural pentose sources. For example, agricultural waste streams based on oat hulls, corn cobs, and sugar cane bagasse can be used.[21] When converting 2-methylfuran (**4**, being readily accessible from furfural) in a Diels-Alder reaction with maleic anhydride (**5**), which also represents a bio-based building block being accessible by fermentation, the resulting cycloalkene derivative **6** is formed, which can subsequently be transformed *via* hydrogenation into the desired cyclic anhydride **7**. Final ring-opening and esterification with 2 equivalents of 2-ethylhexanol (**8**) then furnishes the first desired bio-based plasticizer *exo*-candidate **1**. The formation of the thermodynamically more stable *exo*-diastereomer **6** (over the kinetically favored *endo*-diastereomer) in this type of Diels-Alder reaction is in accordance with experimental and theoretical literature studies for the related Diels-Alder reaction of furan with maleic anhydride.[22] In this study it has been shown that the preference for the *exo*-product is due a low thermodynamic stability of the Diels-Alder adduct, which results in a *retro*-Diels-Alder reaction, thus favoring then the formation of the thermodynamically more stable *exo*-product.[22] For the subsequent ring-opening and esterification step, the alcohol **8** was chosen to allow a comparison with the standard plasticizer DEHP. The stereochemically opposite *endo*-compound **2** as a second target molecule is obtained through an initial Diels-Alder reaction of 2-methylfuran (**4**) and maleate **9** and subsequent hydrogenation of the resulting cycloalkene **10**, yielding the *endo*-product **2**. Note that maleate **9** is also fully available from bio-based raw materials (Scheme 2).

When realizing these synthetic concepts in our laboratory, the initial Diels-Alder reaction of 2-methylfuran (**4**) with maleic anhydride (**5**) was carried out analogously to our previous studies and literature under solvent-free conditions.[19,23,24] Without isolating the formed Diels-Alder adduct **6**, subsequent hydrogenation at 80 bar of H_2 in the presence of 2 wt% of Pd/C as a catalyst and 2-methylfuran as a solvent (leading to a substrate concentration of 2.5 M) gave anhydride **7** in 52% yield after recrystallization. This intermediate **7** was then further converted with alcohol **8** to the desired methyl-substituted bicyclic *exo*-type diester **1**, which was obtained after a straightforward work-up (for details, see Supporting Information) in 58% yield and with a purity of 96% according to GC analysis (Scheme 3). Note that this compound **1** has been obtained as an oil as the preferred form for an application as a plasticizer.



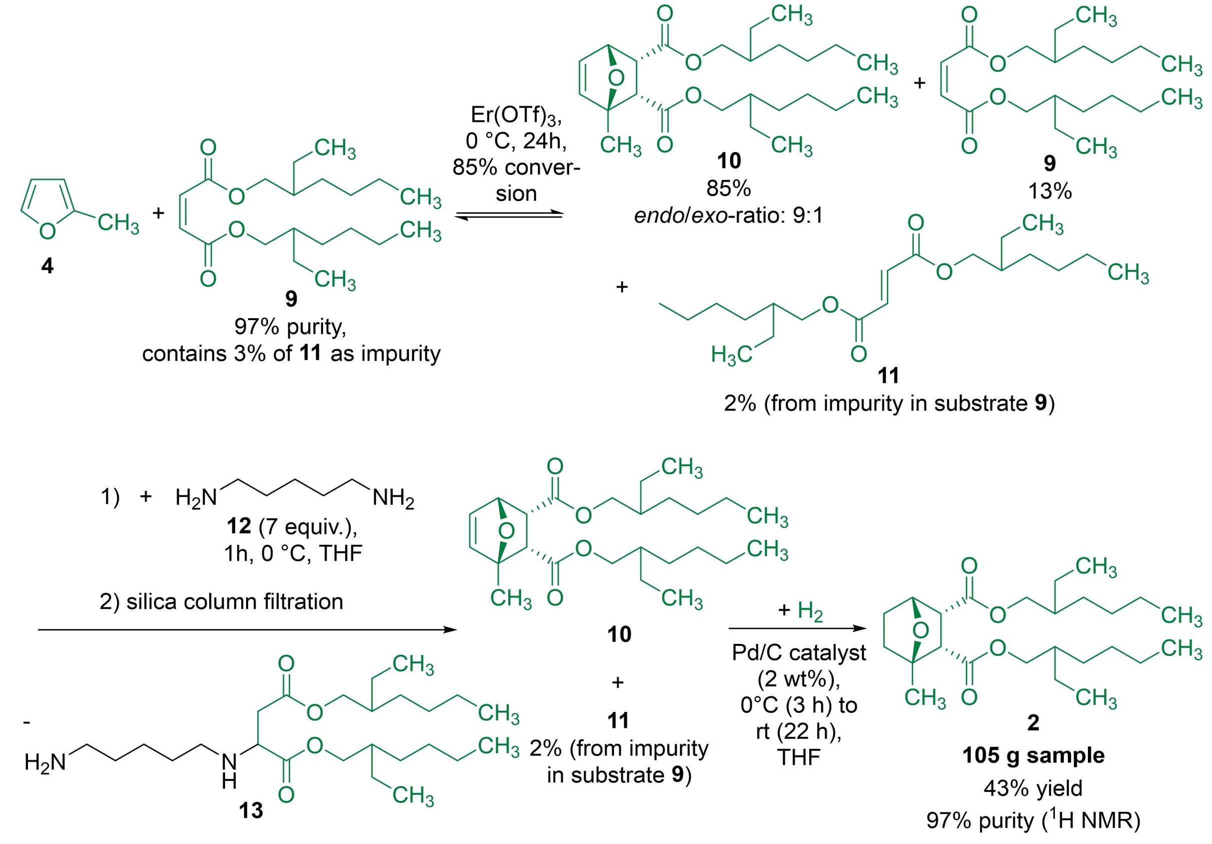
Scheme 3. Synthesis of first bio-based (*exo*-type) target plasticizer **1** (in case of the racemates **1**, **6** and **7**, only one enantiomeric form of the heterocyclic diester substructure is graphically shown).

To gain insight into the relationship of the stereochemistry and plasticizer performance of the new bio-based plasticizer candidates, we then focused on the synthesis of the analogous *endo*-isomer **2** (Scheme 4). As in the Diels-Alder reaction of 2-methylfuran (**4**) and maleic anhydride (**5**) running under kinetic control[25] exclusively the *exo*-adduct **6** is formed, we changed the reagent from anhydride **5** to the maleic diester **9**, which is easily accessible from bio-based raw materials (as shown in Scheme 2). When starting from **9** in the presence of a Lewis acid catalyst, the resulting Diels-Alder reaction preferably gives the *endo*-isomer **2** (Scheme 4).

Since different properties are expected with an altered stereochemical configuration,[26] the different selectivities of the synthetic routes provide a good way to evaluate the influence of the *endo*/*exo* configuration later in the plasticizer performance tests. In order to identify the most suitable Lewis acid for the desired *endo*-selective Diels-Alder reaction of **4** and **9** and having been inspired by the work of Hayashi *et al.*,[27] an initial catalyst screening of different types of Lewis acids was carried out (results not shown). The highest conversion (85 %) to the desired product **10** with an *endo*/*exo*-selectivity of 9 : 1 was found for Er(OTf$_3$) when using this Lewis acid at a catalyst loading of 6 mol% in 10 equivalents of furan **4** at 0 °C for 24 h.

From the crude product of **10**, the remaining furan substrate **4** was evaporated under reduced pressure and Pd/C as well as THF were added for the subsequent hydrogenation step. A hydrogen atmosphere of 1 bar was applied, and the mixture was stirred for 24 h at room temperature. After solvent removal and filtration, the obtained crude product of **2** was purified *via* column chromatography.

However, this turned out to be a bottleneck for further scale-up, as a simple and scalable separation of the side product di(2-ethylhexyl) succinate (being formed in the hydrogenation step from unreacted maleate **9**) from the desired product **2** turned out to be challenging. We could solve this issue by removing the unreacted maleate **9** in the crude intermediate product of **10** *via* an *aza*-Michael addition with pentane-1,5-diamine (**12**, which also represents a bio-based compound) and simple silica gel filtration of adduct **13** after the Diels-Alder reaction (Scheme 4). This method turned out as an efficient way for the purification of **10** prior to column chromatography. The *aza*-Michael reaction only occurred with the maleate **9** and interestingly not with its corresponding fumarate **11** (which represents a non-converted impurity component from the maleate substrate **9**, which is a commercial sample with a purity of 97 %) or the desired Diels-Alder *endo*-intermediate **10**. As the commercially available maleate contains 3 % of fumarate **11**, this impurity remains in the purified product. The desired *endo*-type plasticizer product **2** could be finally isolated after hydrogenation at first 0 °C for 3 h and then 22 h at room temperature, and obtained in 105 g (corresponding to 43 % yield) with 97 % purity (determined by ^{1}H NMR spectroscopy).



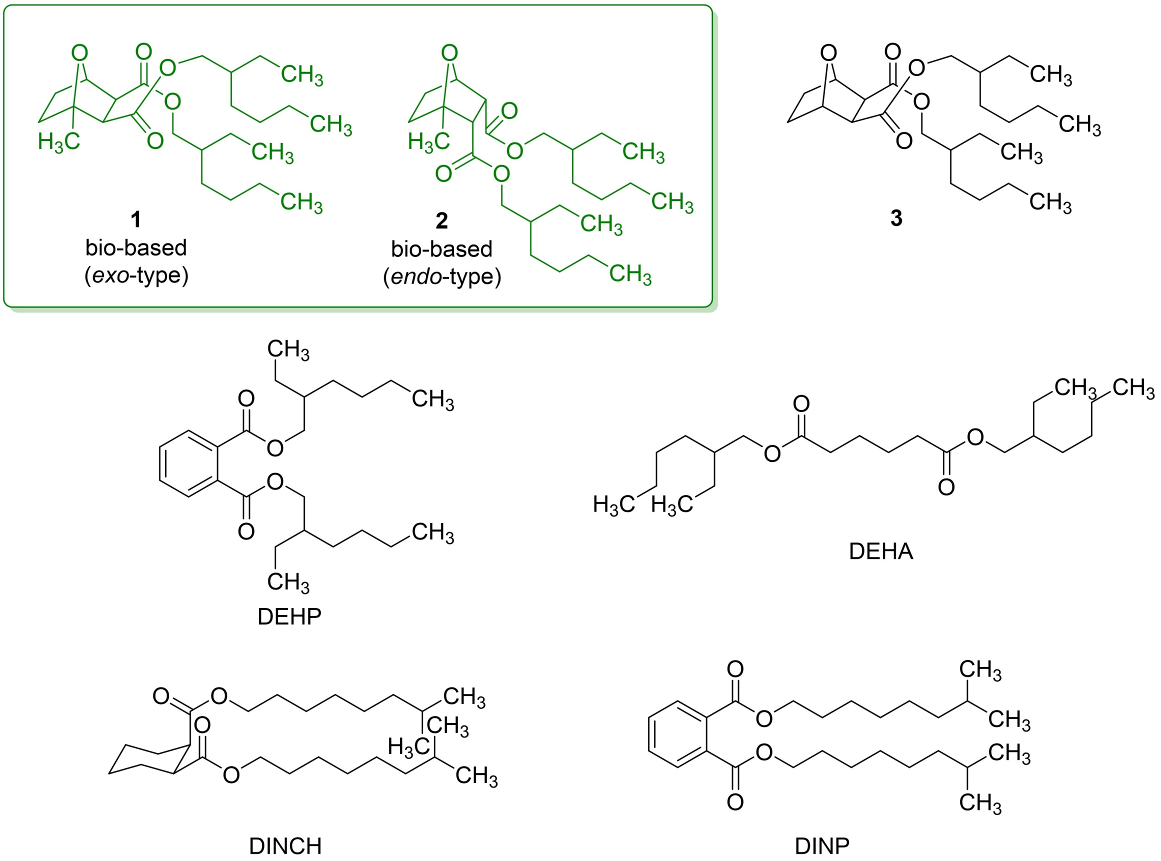
Scheme 4. Synthesis of the second bio-based (*endo*-type) target plasticizer **2** (in case of the racemates **2** and **10**, only one enantiomeric form of the heterocyclic diester substructure is graphically shown).

For comparative studies in the subsequent plasticizer performance tests, we also prepared the non-methyl-substituted (and non-bio-based) *exo*-type furan derivative **3** (Scheme 1 and Scheme 5) as a further product. This synthesis is based on the use of commercially available norcantharidin as starting material. The conversion with 2-ethylhexanol under acid catalysis furnished this reference compound **3** in 80 % yield and with a purity of 96 % according to GC analysis. The work-up was done in analogy to our protocol developed for the *exo*-product **1**, and the whole synthesis of **3** is described in detail in the Supporting Information. It is noteworthy that this non-methylated compound **3** crystallized already below 35 °C in contrast to the bio-based candidate **1**, which was obtained as an oil. This illustrates the positive impact of the methyl-substituent (as a result of the structure of the bio-based raw material for **3**) for reaching the desired oily form for an application as a plasticizer product.

Having the new bio-based plasticizer candidates **1** and **2** as well as the non-methylated derivative **3** as a reference compound in hand, the properties and processibility were investigated. Furthermore, the performance in PVC was tested. For norcantharidin diester **3**, some properties, as the viscosity at 20 °C, could not be measured because of the high melting point. However, all compounds were tested for their suitability as a plasticizer for PVC. The obtained values are compared with the properties of the standard plasticizers DEHP, DEHA (DOA) and DINCH (and the structures of these commercial compounds are also shown in Scheme 5).

First, physical parameters were tested to investigate the processability of the new bio-based plasticizers **1** and **2**. As an important indicator for the gelating properties of a plasticizer, the solution temperature of **1**, **2** and **3** has been determined and compared to those of DEHP, DINP (diisononyl phthalate), DINCH (diisononyl 1,2-cyclohexane dicarboxylate; *cis*/*trans* 90 : 10) and DEHA (Figure 2a). With a solution temperature of 96 °C respectively 95 °C, both compounds **1** and **3** are potential "fast fusers", which means good plasticizing activity due to fast gelation of a plastisol with PVC.[28] Surprisingly, in this case the methyl group (as a substituent caused by the structure of the bio-based raw material) seems not to affect the solution temperature. This stands in sharp contrast to the dramatic effect, which we could recently show for the formal insertion of a methyl group into DEHP.[19] Furthermore, in case of **1** (and also for the reference compound **3**) the bicyclic structure seems to have a beneficial effect on the solution temperature in comparison with the standard plasticizer DEHP.

Thus, in this initial use test study the *exo*-configured compound **1** shows a very promising solution temperature as well as good compatibility with PVC. In contrast, the *endo*-compound **2** with an opposite diastereomeric structure showed



Scheme 5. Structure of investigated plasticizers in consideration of their 3D-structure. DEHA (DOA): di(2-ethylhexyl) adipate (dioctyl adipate). In case of the racemates **1** and **2**, only one enantiomeric form of the heterocyclic diester substructure is graphically shown.

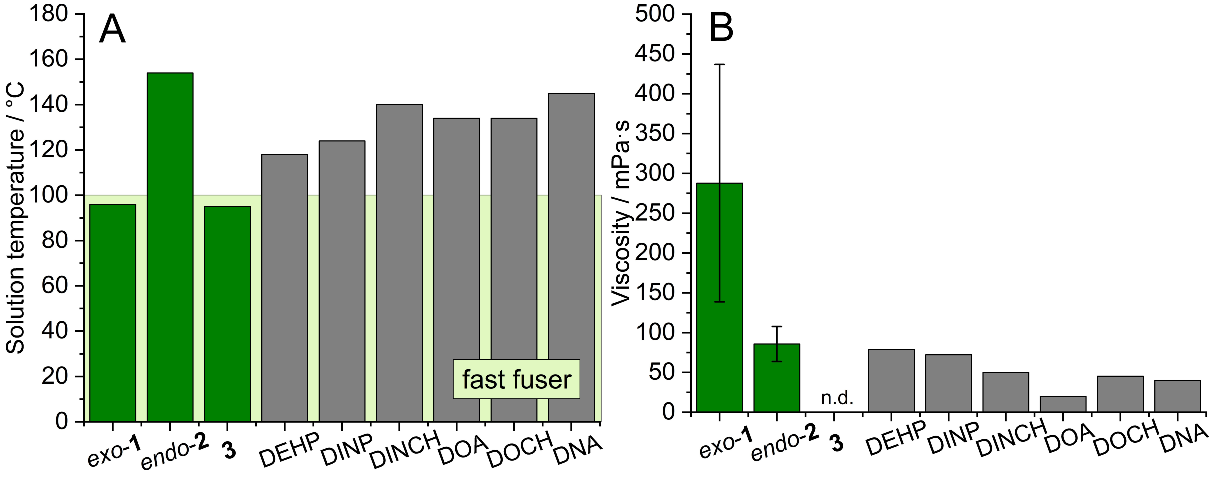


Figure 2. Physical properties of tested plasticizer candidates (green) in comparison to known compounds (DOCH: di(2-ethylhexyl) 1,2-cyclohexane dicarboxylate (dioctyl 1,2-cyclohexane dicarboxylate); DNA: diisononyl adipate). a) Solution temperature. b) Viscosity at 20 °C. n.d.: not analyzed because of high melting point. Error bars show standard deviation of the measurement of two separate batches.

a high solution temperature of 153 °C. As the compounds **1** and **2** only differ in the *exo*/*endo*-configuration, the three dimensional structure seems to have a dramatic effect on this property (which is widely known for pharmaceuticals but a less studied effect in the field of bulk chemicals in general and plasticizers in particular). The high impact of stereochemistry also for plasticizer properties can be seen by the comparison of DINCH with DINP as well. Here, DINCH with its sterically more demanding structure shows a higher solution temperature as the corresponding aromatic DINP.

In Figure 2b, the viscosity of typical plasticizers and the new compounds is shown as a process parameter for applicability. The viscosity of compound **1** is significantly higher than that of all other compounds. This, however, is a drawback and task for optimization since it is more difficult to process viscous oils. A huge difference between the first (183 mPa s) and the second batch (392 mPa s) was measured. This may be caused by different purification steps and therefore different solvent content and impurities. Nevertheless, both values exceed the viscosity of DEHP with 82 mPa s dramatically. However, the change of stereochemistry seems to cause a significant improvement with a viscosity of 70 mPa s for the *endo*-compound **2**. Thus, while the *exo*-compounds **1** and **3** show good solution temperatures, the viscosity of the *endo*-isomer **2** is already in a sufficient range.

To investigate the performance of the bio-based plasticizers **1** and **2**, formulations of 100 parts PVC, 60 parts plasticizer and 2 parts of stabilizer were processed. The resulting soft PVC formulations were obtained successfully as flexible and transparent foils when using both new products being accessible from bio-based feedstocks, namely the *exo*-plasticizer **1** as well as the *endo*-plasticizer **2** (Figure 3).

When studying further performance parameters with the new bio-based plasticizers **1** and **2**, we were pleased to find that the investigated plasticizers show excellent compatibility with PVC and that the efficiency of the *exo*-compound **1** is even better than that of today's commercialized products DINP or Hexamoll® DINCH, which can be seen in the low Shore A value (Figure 4).

As also reference compound **3** gave similar results, the methyl-substituent appears to play not a significant role for this performance parameter. Probably due to the less optimal

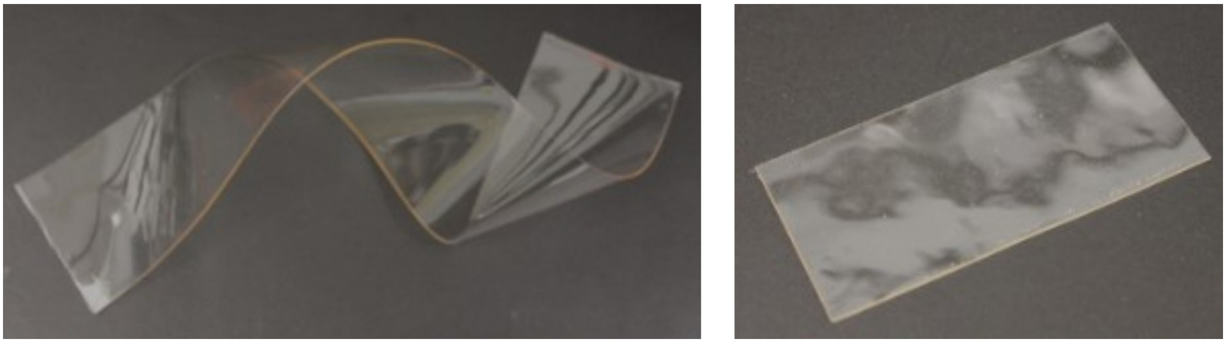


Figure 3. Soft PVC formulated with the new bio-based plasticizers **1**.

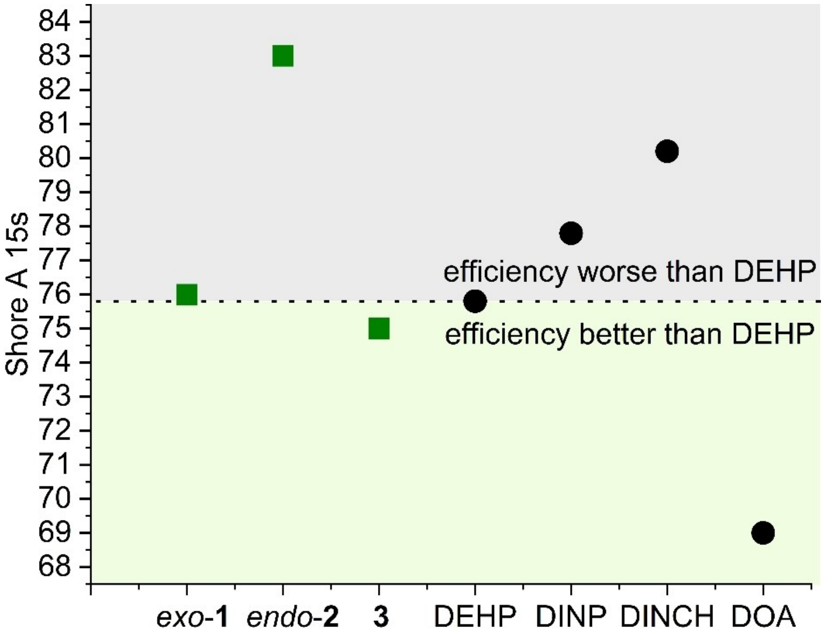


Figure 4. Efficiency of plasticizers determined by comparison of hardness according to Shore A.

configuration of the *endo*-isomer **2**, its efficiency is significantly lower compared to the *exo*-isomer **1** as well as the commercial plasticizers. The whole results of this comparison study with DEHP as benchmark are visualized in Figure 4.

Furthermore, the tensile strength of the bio-based plasticizers **1** and **2** was investigated (Figure 5). It is noteworthy that for all three PVC formulations the performance of the *exo*-isomer **1** and *endo*-isomer **2** again differ significantly from each other, which once more underlines the significant effect of stereochemical properties on plasticizer performance. On the other hand, except for the modulus of elasticity, the influence of the biorenewable-based methyl group seems to be less significant as can be seen by the comparison of **1** with the non-methyl-substituted analogue **3**. Furthermore, all of these values obtained with the new bio-based plasticizer molecules **1** and **2** are in the same order of magnitude as for standard plasticizers. This underlines the principal suitability of the new bio-based compounds **1** and **2** as plasticizers.

When studying the tensile stress, the PVC-formulations containing *exo*-compound **1** as well as the non-methyl-substituted analogue **3** break at lower tensile stress in comparison to the cyclic plasticizers DEHP, DINP and DINCH. By changing the stereochemical properties, however, a much higher tensile stress could be applied before breaking as can be seen from the highest value which was obtained when using the *endo*-type molecule **2** (Figure 5a).

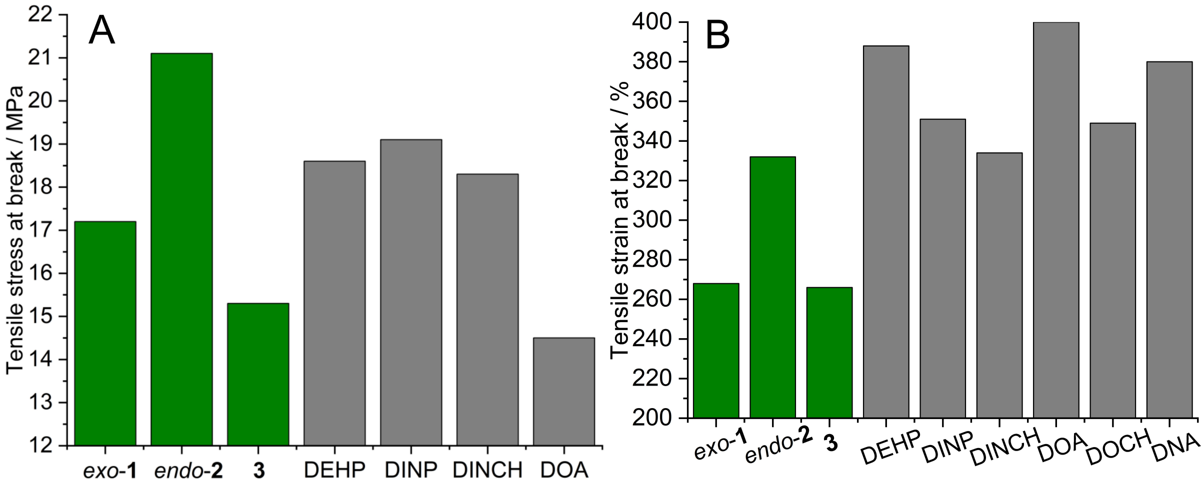


Figure 5. Tensile strengths of the developed products in comparison to known plasticizers (DOCH: di(2-ethylhexyl) 1,2-cyclohexane dicarboxylate (dioctyl 1,2-cyclohexane dicarboxylate); DNA: diisononyl adipate). a) Tensile stress at break. b) Tensile strain at break.

However, the tensile strain at break of the new *exo*-candidate **1** (and the *exo*-analogue **3**) is slightly lower compared to the known plasticizer molecules (Figure 5b). As the values of 268 % (**1**) and 266 % (**3**) can be considered identical (when taking into account the deviation of this test method), the additional methyl group in **1** does not seem to influence this value. However, it is again noteworthy that the changed structure from *exo* to *endo* affects the tensile strain extremely as a dramatically increased, attractive value of 332 % was measured for the bio-based *endo*-compound **2** (Figure 5b).

In summary, the *exo*-compounds **1** and **3** show excellent compatibility with PVC, resulting in a soft material comparable to PVC plasticized with DEHP. On the other hand, the tensile strength is less advantageous. Here, interestingly the *endo*-compound **2** showed to be more effective, while this compound showed lower efficiency. It was expected that the stereochemical configuration of the molecules plays an important role in the performance, as it can be seen for *cis*/*trans*-DINCH.[26] But the magnitude of this effect is surprising, as it exceeds the influence of an additional methyl group. For comparison, there is a significant increase of the solution temperature by a formal introduction of a methyl group, which we could observe in our previous investigations.[19]

The volatility (defined as the relative loss of mass from a specimen over a period) of the new candidates is below the one of DEHA (DOA) but still relatively high when considering the molecular weight. The volatility of the *exo*-type reference compound **3** with 2.59 % loss of mass at 130 °C for 24 h corresponds to that of Hexamoll DINCH with 2.48 %, which is higher than the volatility value of DINP. The volatility of 3.35 % for the methyl-substituted *exo*-variant **1** can be considered too high for a high-temperature application. This value correlates with the molecular mass of plasticizers, as can be seen in Figure 6. This is in good accordance with the literature.[27] A slightly higher volatility (5.51 %) could be found for the *endo*-candidate **2**, which can partly be attributed to the impurity of succinic ester.

The HCl-resistance of the *exo*-compounds was slightly lower (**1**: 9 min 24 s, **3**: 9 min 17 s) than for the commercial examples (DINCH: 17 min 2 s), but still in an acceptable range. Here again, the *endo*-configuration seems to be advantageous (**2**: 18 min 17 s), and this stability of **2** turned out to be already on the same level as the ones for commercial options (data shown in the Supporting Information).

In addition, the cold break temperature represents a further important parameter for plasticizers. The formulation containing the bio-based bicyclic ester **1** was analyzed by dynamic mechanical analysis and showed a glass transition temperature of +1 °C, which limits the possibility of application. For the films containing the compounds **2** and **3**, the cold-break temperature was determined, which corresponds approximately to the glass transition temperature. Compound **3** led to a brittleness temperature of −10 °C of the PVC. Change of the configuration to *endo*-product **2** led to a dramatically lower brittleness temperature of −27.5 °C. This, however, is still relatively high in comparison with commercial plasticizers (DINCH: −42.5 °C, DINP: −35.0 °C). In comparison to *ortho*-phthalates, the new compounds show a three-dimensional "backbone structure". Furthermore, they differ from the cyclohexanoic acid diesters by their rigid framework. These structural differences may cause the less performant low-temperature properties. For similar *endo*-compounds bearing a bridging methylene group instead of the oxygen, very good low-temperature behavior is described in the literature with a cold break temperature of −55 °C.[29] This underlines the tremendous effect of the oxo-bridge. The low-temperature properties, however, can potentially be tuned by choosing a longer or linear side chain alcohol.[9]

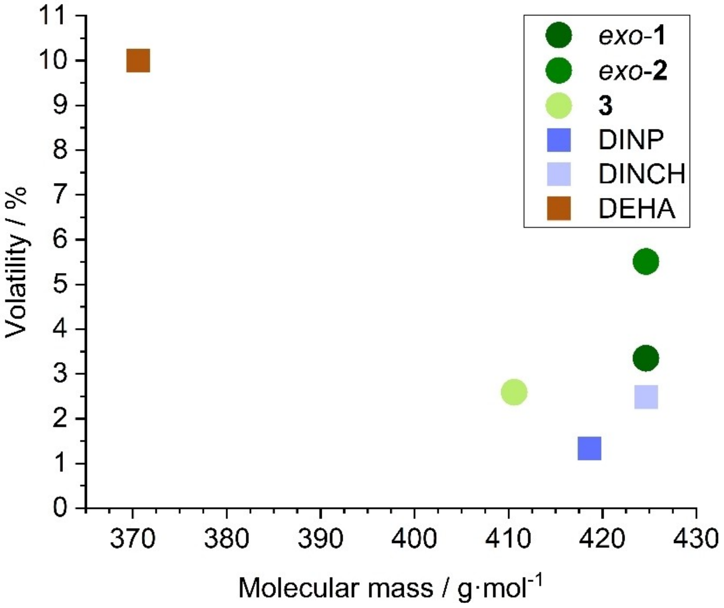


Figure 6. Volatility of different plasticizers in soft PVC formulations against their molecular mass.

Conclusion and Outlook

The synthesis of the bicyclic oxo-bridged diesters **1** and **2** offers a new and fully bio-based product platform for the important industry segment of plasticizers. The bio-based *exo*-type lead structure **1** was successfully synthesized starting from 2-methylfuran (**4**) and maleic anhydride (**5**). In a sequential one-pot process, the corresponding anhydride **6** was synthesized and could be esterified with 2-ethylhexanol, thus furnishing the desired product **1**. To evaluate the influence of both the additional methyl group and the oxo-bridge, the analogue ester **3** was synthesized. Furthermore, the corresponding *endo*-compound **2** was synthesized to reveal the effects of stereogenic configuration.

In plasticizer performance tests, the new bio-based compounds **1** and **2** show opposite effects, depending on their *exo*/*endo*-configuration. While the *exo*-compound **1** shows a very promising solution temperature and good efficiency as a plasticizer for PVC, the *endo*-configuration of **2** resulted in more advantageous viscosity, tensile strength and low-temperature properties. In contrast to **1**, the higher symmetry of the non-bio-based reference compound **3** results in a high melting point, which is disadvantageous for a plasticizer application and made the measurement of the viscosity impossible. All in all, the three-dimensional structure of the plasticizer showed to be the most influential variable on the performance of the plasticizer and the resulting PVC-formulation. Furthermore, a comparison of the new plasticizer compounds **1** and **2**, which are accessible from bio-based resources, with the known and at least to the most extent petrochemically derived plasticizer compounds enabled an insight into structure-activity relationships. In general, these studies also revealed promising plasticizer properties. For example, the *exo*-configured compound **1** shows an attractive solution temperature fulfilling the criterium for a “fast fuser” as well as good compatibility with PVC.

For future work, a mixture of the bio-based compounds **1** and **2** can be considered as a promising tool to benefit from the advantages of both isomers for different plasticizer parameters, thus leading to synergistic effects and superior properties of such a “blended” fully bio-based plasticizer system. In addition, process development and optimization of, e.g., downstream-processing is a further task of future research work in order to obtain a sustainable synthetic access to the target molecules with favorable metrics related to the sustainability of a process such as the E factor[30] (Environmental factor) as one of them.

Experimental Section

Synthesis of racemic *bis*(2-ethylhexyl) (1*R**,2*R**,3*S**,4*R**)-1-methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (1)

In an open round-bottom flask (3a*R**,4*R**,7*R**,7a*S**)-4-methylhexahydro-4,7-epoxyisobenzofuran-1,3-dione (**7**, 34 g, 186 mmol; prepared as described in Supporting Information) was stirred with 2-ethylhexanol (86 mL, 560 mmol) and H_2SO_4 (1.02 mL, 1.87 mmol) at 90 °C for 24 h. The reaction mixture was dissolved in EtOAc, washed once with saturated $NaHCO_3$ solution and once with saturated NaCl solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The excess of alcohol was distilled off (**4** 10^{-3} mbar, 45 °C). After filtration over aluminum oxide (neutral, 2 cm, rinsing with cyclohexane), the desired racemic *exo*-product *bis*(2-ethylhexyl) (1*R**,2*R**,3*S**,4*R**)-1-methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (**1**, 46 g, 58 %) was obtained as yellowish oil. ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 5.03$ (d, ${}^{3}J = 5.2$ Hz, 1 H, C(6)H), 4.04–3.81 (m, 4 H, C(1′)H) 3.10 (d, 3 J = 9.6 Hz, 1 H, C(1)H) 2.29 (d, ${}^{3}J = 9.6$ Hz, 1 H, C(2)H) 1.90 (dp, ${}^{2}J = 11.9$ Hz, ${}^{3}J = 5.7$, 4.8 Hz, 1 H, C(5)H), 1.68 (dp, ${}^{2}J = 13.4$ Hz, ^{3}J = 9.7, 5.1 Hz, 1 H, C(4)H), 1.64–1.47 (m, 4 H, C(4 + 5 + 2′)H), 1.46 (s, 3 H, C(9)H), 1.40–1.20 (m, 16 H), 0.94–0.80 (m, 12 H, C(6′ + 2“)H). ^{13}C-NMR (126 MHz, $CDCl_3$): $\delta =$ 171.32 (C(7)), 171.13 (C(8)), 85.83 (C(3)), 77.25 (C(6)), 67.51 (C(1′)), 67.33 (C(1′)), 56.23 C(1), 53.26 C(2), 38.78 (Alkyl), 38.75 (Alkyl), 38.72 (Alkyl), 38.69 (Alkyl), 36.84 (C(4)), 31.08 (C(5)), 30.48 (Alkyl), 30.45 (Alkyl), 30.42 (Alkyl), 30.39 (Alkyl), 29.14 (Alkyl), 29.06 (Alkyl), 29.01 (Alkyl), 28.99 (Alkyl), 23.92 (Alkyl), 23.84 (Alkyl), 23.80 (Alkyl), 23.75 (Alkyl), 23.10 (Alkyl), 18.39 (C(9)), 14.19 (C(6′)), 11.10 (C(2″)), 11.08 (C(2“)), 11.02 (C(2″)). IR: 2955 (m), 2927 (m), 2873 (w), 2860 (w), 1742 (s). HRMS (ESI): calculated for $[C_{25}H_{44}O_5H^+]$: 447.3081, found: 447.3082, deviation: 0.22 ppm.

Synthesis of racemic *bis*(2-ethylhexyl) (1*R**,2*S**,3*R**,4*R**)-1-methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (2)

In a jacked reactor (2 L, glass) equipped with an overhead stirred, 2-methylfuran (**4**, 750 mL, 8.31 mol) was chilled to 0 °C. Then, *bis*(2-ethylhexyl) maleate (**9**, 276.7 g, 0.813 mol) was added and the yellow solution stirred for 30 min. Erbium(III) triflate (31.17 g) was added to give a yellow solution which was stirred at 270 rpm at 0 °C for 22 h. After stirring, the reaction was quenched with saturated Na_2CO_3 solution (250 mL) to give a foamy pink aqueous suspension and a yellow organic solution. The organic solution was separated, dried over $MgSO_4$ and filtered. Finally, excess 2-methylfuran (**4**) was removed (10 mbar, 40 °C) to yield a yellow oil. The conversion to the desired product (**10**, 85 %) and the diastereoselectivity (*endo*/*exo*: 9 : 1) were determined by ^{1}H NMR. Subsequently, to a solution of this crude product **10**, which contains *bis*(2-ethylhexyl) maleate (**9**, 13 %) and *bis*(2-ethylhexyl) fumarate (**11**, 2 %), in THF (650 mL), 1,5-diaminopentane (**12**, 50 mL, 0.43 mol) was added. The resulting mixture was stirred at 400 rpm and 0 °C for 1.5 h. After filtration over silica gel (9 cm diameter, 7 cm height) for removal of maleate derivative **13**, the column was flushed with ethyl acetate (200 mL) and then the solvent was removed from the obtained filtrate (1 mbar, 30 °C). The resulting crude product **10**, which still contains *bis*(2-ethylhexyl) fumarate (**11**, 2 %), was dissolved in THF (approx. 500 mL) and palladium on carbon (10 wt % Pd basis, 5 g, 2 wt%). A hydrogen atmosphere was applied (1 bar) and the mixture stirred at 400 rpm at 0 °C. After 3 h, the mixture was allowed to heat to room temperature and stirred for further 22 h. Then, the black suspension was filtered, and the solvent was removed from the clear yellow solution. A part (204.36 g) of the resulting oil (total of 290.61 g) was purified in portions *via* column chromatography to give the desired racemic *endo*-product *bis*(2-ethylhexyl) (1*R**,2*S**,3*R**,4*R**)-1-methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylate (**2**, 105.1 g, 97 % ^{1}H NMR purity, corresponding to a theoretical total yield of 43 % over all three reaction steps) as a colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 4.59 (t, ^{3}J = 5.3 Hz, 1 H, C(6)), 4.13–3.94 (m, 2 H, C(1‘)), 3.94–3.79 (m, 2 H, C(1′)), 3.29 (ddd, ^{3,3,4}J = 11.8, 5.1, 1.7 Hz, 1 H, C(1)), 2.91 (dd, ^{3,4}J = 11.8, 2.1 Hz, 1 H, C(2)), 2.16–2.01 (m, 2 H, C(4 + 5)), 1.89–1.75 (m, 1 H, C(5)), 1.55 (s, 3 H, C(9)), 1.54–1.49 (m, 2 H, C(2′)), 1.46–1.37 (m, 1 H, C(4)), 1.37–1.18 (m, 16 H, C()), 0.93–0.80 (m, 12 H, C(2″ + 6′)). ^{13}C-NMR (126 MHz, $CDCl_3$): $\delta = 171.14$ (C(7/8)), 171.03

(C(7/8)), 86.98 (C(3)), 78.33 (C(6)), 67.21 (C(1′)), 67.01 (d, C()), 53.65 (C(2)), 50.50 (C(1)), 38.71 (C(2′)), 32.17 (C(4)), 30.55–30.43 (C(Alk)), 29.08–28.95 (C(Alk)), 27.65 (C(5)), 23.94–23.75 (C(Alk)), 23.08 (C(Alk)), 20.99 (C(9)), 14.15 (C(6′)), 11.04 (C(2′′)). HRMS (ESI): calculated for $[C_{25}H_{44}O_5+Na]^+$ *m/z* (exp) = 447.3077, *m/z* (calcd): 447.30810, deviation: 0.89 ppm.

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