catalysts

MDPI

Article

Plant-Mediated Enantioselective Transformation of Indan-1-One and Indan-1-ol

Wanda Mączka [1,*], Katarzyna Wińska [1,*], Małgorzata Grabarczyk [1,*] and Renata Galek [2]

[1] Department of Chemistry, Wroclaw University of Environmental and Life Science, Norwida 25, 50-375 Wroclaw, Poland

[2] Department of Genetics, Plant Breeding and Seed Production, Wroclaw University of Environmental and Life Science Pl. Grunwaldzki 24A, 53-363 Wroclaw, Poland; renata.galek@upwr.edu.pl

* Correspondence: wanda.maczka@upwr.edu.pl (W.M.); katarzyna.winska@upwr.edu.pl (K.W.); malgorzata.grabarczyk@upwr.edu.pl (M.G.); Tel.: +48-71-320-5213 (W.M. & K.W.)

Received: 24 September 2019; Accepted: 8 October 2019; Published: 12 October 2019

Abstract: The main purpose of this work was to discover the way to obtain pure enantiomers of indan-1-ol. The subject of the study was the ability of the plant enzyme system to reduce the carbonyl group of indan-1-one, as well as to oxidize the hydroxyl group of racemic indan-1-ol. Locally available fruit and vegetables were selected for stereoselective biotransformation. During the reduction, mainly alcohol of the *S*-(+)-configuration with a high enantiomeric excess (ee = 99%) was obtained. The opposite enantiomer was obtained in bioreduction with the apple and parsley. Racemic indan-1-ol was oxidized by all catalysts. The best result was obtained for the Jerusalem artichoke: Over 50% conversion was observed after 1 h, and the enantiomeric excess of unreacted *R*-(–)-indan1-ol was 100%.

Keywords: indan-1-one; indan-1-ol; biotransformation; reduction; oxidation

1. Introduction

In the last decade the need to obtain applicable biologically-active enantiopure compounds has been growing increasingly, because the way they act within living organisms depends largely on their absolute configuration. The chiral environment of a patient's body distinguishes the enantiomers (optical isomers) of drugs as the eutomer (the good enantiomer) and the distomer (the unwanted enantiomer, sometimes with strong side effects). Both enantiomers very probably display different biological properties, and therefore even drugs that are initially administered as the racemate are considered for the development of a single-enantiomer synthesis [1].

Chiral secondary alcohols are increasingly recognized as valuable chiral building blocks in the organic syntheses of pharmaceuticals and agrochemicals. In the past, they were produced by several methods, such as by the use of chiral ligands [2,3], separation by chiral chromatography [4] and the application of chiral metal complexes in the asymmetric reduction of prochiral compounds [5]. All of these processes have their own inherent drawbacks, including difficulty in operation, generation of by-products, exorbitant cost and harmful effects upon the environment [6]. This problem can be solved by biocatalysis, which can additively shorten the synthetic route and enable the achievement of high yields with excellent chemo-, regio- and stereo-selectivity [7].

In the biological approaches using biocatalysts, optically active alcohols are prepared from prochiral ketones [8–11], or racemic alcohols as starting materials [8,12–15]. Biocatalytic desymmetrization using ketones is highly significant in several processes, as this allows one to obtain pure enantiomer in a 100% theoretical yield.

In turn, oxidative kinetic resolution is an efficient process involving the conversion of two enantiomers of alcohol in racemic mixtures into ketones at different rates, so that only one of the enantiomers remains. This process is limited in yield, because only one enantiomer undergoes the reaction, which results in a theoretical maximum 50% of pure enantiomer [16].

Both reactions—the reduction of ketones and the oxidation of alcohols—can be catalyzed by oxidoreductases, mainly alcohol dehydrogenases. These enzymes are NAD^+- or $NADP^+$-dependent, therefore cofactor recycling is an essential component of the reaction mixture [17]. The use of the intact plant system instead of plant cells or isolated enzymes offers several considerable advantages: Their availability at low cost, they are easily disposable as biodegradable, and they have mild reaction conditions. The easy preparation of the reactive system makes the use of comminuted plant material as a biocatalyst an attractive economic alternative [18]. Plant biocatalysts have been applied primarily in the reduction of ketones. [8–11,19–25]. Biooxidation of alcohols has been described much less [8,12–15,22].

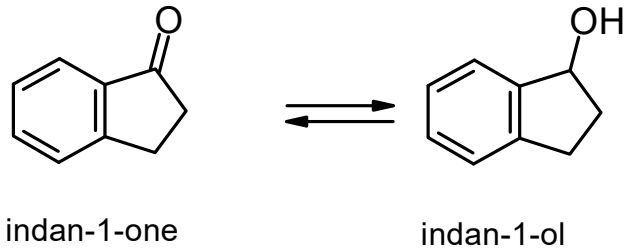
An example of interesting secondary alcohol is indan-1-ol. This compound was observed as a semi-volatile product of *Lemna* sp. [26], and is also a component (8%) of the floral essential oil of *Guettarda poasana* (*Rubiaceae*) [27]. A derivative of indanol, which was isolated from a culture of *Ganoderma applanatum*, was found to supress the growth of *Fusobacterium nucleatum*—a prominent member of the oral microflora implicated in periodontitis [28]. The analog of indanol—(1*S*,2*R*)-1-amino-2-indanol—is a key intermediate in the synthesis of Indinavir (Crixivan®), which acts as the HIV protease inhibitor in antiretroviral therapy. Although it contains five chiral centers with 32 possible stereoisomers, only a single stereoconformation of Indinavir confers the desired therapeutic effect [29,30]. Chiral aminoindanol is an valuable substrate in the preparation of other chiral auxiliaries used in asymmetric synthesis [29,31]. Indatraline, an analog of indanol, is used in the treatment of cocaine addiction [32]. In turn, PT285 and PT2877 are second-generation inhibitors of the hypoxia-inducible factor 2α (HIF-2α) and the key oncogenic driver in renal carcinoma [33]. Based on the literature data [21,34–37], only a few biocatalytic methods have been employed to obtain the indan-1-ol enantiomers. Nevertheless, kinetic resolution of indan-1-ol has been elegantly performed using sequential combinations of lipase-catalyzed resolution and Mitsunobu inversion [37].

The information presented above encouraged us to attempt research into transformations of indan-1-one and indan-1-ol by means of the enzymatic system of comminuted plant parts.

2. Results and Discussion

2.1. Reduction of Indan-1-One Using the Plant Enzymatic System

In 2018, Bennamane et al. [21] published a paper where the authors biotransformed indan-1-one by *Zingiber officinale* and *Citrus reticulata*. In addition, the ability of carrot to stereoselectivly reduce prochiral ketones has been very well documented in the literature (also in our team's research). The above premises prompted us to undertake research on the stereoselectivity of the biotransformation of indan-1-one and indan-1-ol via biocatalysts readily available in our latitude (Scheme 1).



Scheme 1. The plant biotransformation of indan-1-one and indan-1-ol.

In total, we used 11 plant biocatalysts to transform both compounds: Nine vegetables (*Apium graveolens* L.—celeriac, *Daucus carota* L.—carrot, *Petroselinum crispum* L.—parsley, *Pastinaca sativa* L.—parsnip, *Beta vulgaris* L.—beet, *Helianthus tuberosus* L.—Jerusalem artichoke, *Solanum tuberosum*

L.—potato, *Allium ampeloprasum* L.—leek, *Raphanus sativus* L.—radish) and two fruit *Malus pumila* L.—apple and *Cydonia oblonga* Mill.—quince.

The initial identification of the obtained product was made by means of gas chromatography. The order of the signals was assigned based on a comparison with the standards (Figure 1). Assignment of the alcohol configuration was made based on measuring the specific rotation and comparison with the pertinent literature data.

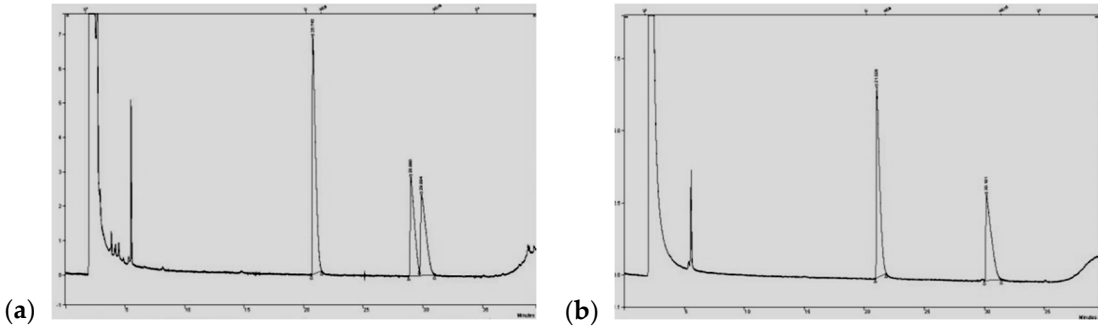


Figure 1. Chromatograms of the standards and biotransformation: (**a**) Indan-1-one t_R = 20.7 min., *S*-(+)-indan-1-ol t_R = 28.9 min., *R*-(–)-indan-1-ol t_R = 29.9 min., (**b**) biotransformation of indan-1-ol by the Jerusalem artichoke.

Reactions were carried out with the aid of the crushed flesh of the above-mentioned plants suspended in a phosphate buffer of the appropriate pH. The obtained results of the indan-1-one biotransformations are presented in Table 1.

Table 1. Results of the indan-1-one plant biotransformations determined by GC analysis of the crude extract.

Biocatalyst	% of Alcohol	ee [%]
A. ampeloprasum L. (leek)	0	0
A. graveolens L. (celeriac)	8.4	99 *R*-(−)
B. vulgaris L. (beet)	0	0
D. carota L. (carrot)	8.5	99 *S*-(+)
H. tuberosus L. (Jerusalem artichoke)	3.6	99 *S*-(+)
P. sativa L. (parsnip)	7.4	99 *S*-(+)
P. crispum L. (parsley)	8.4	99 *S*-(+)
R. sativus L. (radish)	0	0
S. tuberosum L. (potato)	0	0
M. pumila L. (apple "Gloster")	3.1	99 *R*-(−)
C. oblonga Mill. (quince)	0	0

Six biocatalysts were found capable of reduction of indan-1-one with an excellent enantioselectivity (ee = 99.9% *S*(+)) but, unfortunately, with a low yield. The best result was obtained by means of the enzymatic system of comminuted plants representing the *Umbelliferae* family (*Apiaceae*, e.g., celery, carrot, parsley), which reduced indan-1-one with a yield at the level of about 8%. We received extremely interesting results for one of the vegetables—the celery. The enzyme system of this vegetable biotransformed the substrate into alcohol with a configuration which did not agree with the Prelog rule. Although *R*-(−)-indan-1-ol was also obtained using the apple as the bioreagent, the efficiency of this process was low.

In 2019, Nagaki et al. [34] biotransformed indan-1-one in a calli culture of *D. carota*. After 25 days, they obtained only 26% alcohol. In turn, in a work by Bennamane et al. [21], indan-1-one was reduced by *Zingiber officinale* and *Citrus reticulata* with a higher yield (36% and 43%, respectively) but lower stereoselectivity (26% *S*-(+) and 95% *S*-(+), respectively).

2.2. Oxidation of Indan-1-ol Using the Plant Enzyme System

Since the indan-1-one reduction efficiency by means of comminuted plants was so very low, we tried to transform the corresponding racemic alcohol. Stereoselective oxidation of alcohols has useful applications in organic synthesis, but it is less popular than the reduction of ketones in biotransformations [13]. So far, biooxidation has been described almost exclusively for model substrates such as 1-phenylethanol and its derivatives. Andrade et al. [14] selected 15 plants to carry out the biooxidation of (*RS*)-1-phenylethanol and its derivatives. During the biotransformation of racemic 1-phenylethanol by means of *Zingiber officinale* and *Polymnia sonchifolia*, cyclic deracemization was observed, when the biocatalyst promoted an enantioselective oxidation of the alcohol *S*-enantiomer, and the product was reduced by the *S*-selective enzyme. After six days the authors obtained 100% of 1-phenylethanol with ee = 98% (*S*) (*Z. officinale*) and 99% with ee = 93% (*S*) (*P. sonchifolia*). Further, in the case of (*RS*)-1-(4-bromophenyl)ethanol oxidation, the best biocatalyst was *Dioscorea alata*. The (*R*)-enantiomer was oxidized into the corresponding ketone in 53%, leaving the (*S*)-1-(4-bromophenyl)ethanol unreacted with ee = 83%. Next, the 1-phenylethanol derivative (*RS*)-1-(4-methylphenyl)ethanol was oxidized by *Solanum tuberosum*, and after 3 days of transformation gave (*R*)-1-(4-methylphenyl)ethanol with ee = 86% and a yield of 32% [14].

The Jerusalem artichoke oxidized racemic 1-phenylethanol and 1-(2-naphthyl)ethanol very stereoselectivly, yielding 58% of *R*-1-phenylethanol (ee = 80%) and 54% of *R*-1-(2-naphthyl)ethanol (ee = 95%) [12]. When comparing the oxidations of 1- and 2-naphthalene derivatives [8], the β-position was revealated to be more suitable for enzymatic reaction because, similarly to the Jerusalem artichoke, the celeriac enzymatic system transformed 1-(2-naphthyl)ethanol in 60% with a 35% enantiometic excess *S*-(–)-enantiomer of unreacted alcohol, but the other alcohol with biaryl ring, that is, 1-(1-naphthyl)ethanol, was not transformed.

In our research, the same plants were used both for the biooxidation and reduction of indan-1-one. The obtained results of the indan-1-ol biotransformations are presented in Table 2.

Table 2. Results of the indan-1-ol plant biotransformations determined by GC analysis of the crude extract.

Biocatalyst	Ketone [%]	The Unreacted Alcohol	
		%	ee [%]
A. ampeloprasum L. (leek)	2.5	97.5	1.2 *S*-(+)
A. graveolens L. (celeriac)	44.4	55.6	4.4 *S*-(+)
B. vulgaris L. (beet)	30.8	69.2	12.8 *R*-(−)
D. carota L. (carrot)	16.1	83.9	12.8 *S*-(+)
H. tuberosus L. (Jerusalem artichoke)	99.5	0.5	99 *R*-(−)
P. sativa L. (parsnip)	28.9	71.2	7.3 *S*-(+)
P. crispum L. (parsley)	31.2	68.8	8.4 *S*-(+)
R. sativus L. (radish)	3.4	96.6	1.3 *S*-(+)
S. tuberosum L. (potato)	17.8	82.2	12.4 *S*-(+)
M. pumila L. (apple "Gloster")	6.2	93.8	3.6 *S*-(+)
C. oblonga Mill. (quince)	4.7	95.3	2.2 *R*-(−)

All biocatalysts were able to oxidize indan-1-ol within 48 h. This transformation was more efficient than the bioreduction of indan-1-one, but less stereoselective. Only in the case of biotransformation with crushed Jerusalem artichoke pulp was complete conversion after 48 h observed. For this reason, we decided to study the course of this biotransformation in time. Samples were taken every 1, 2, 5, 21, 24 and 28 h (Figure 2).

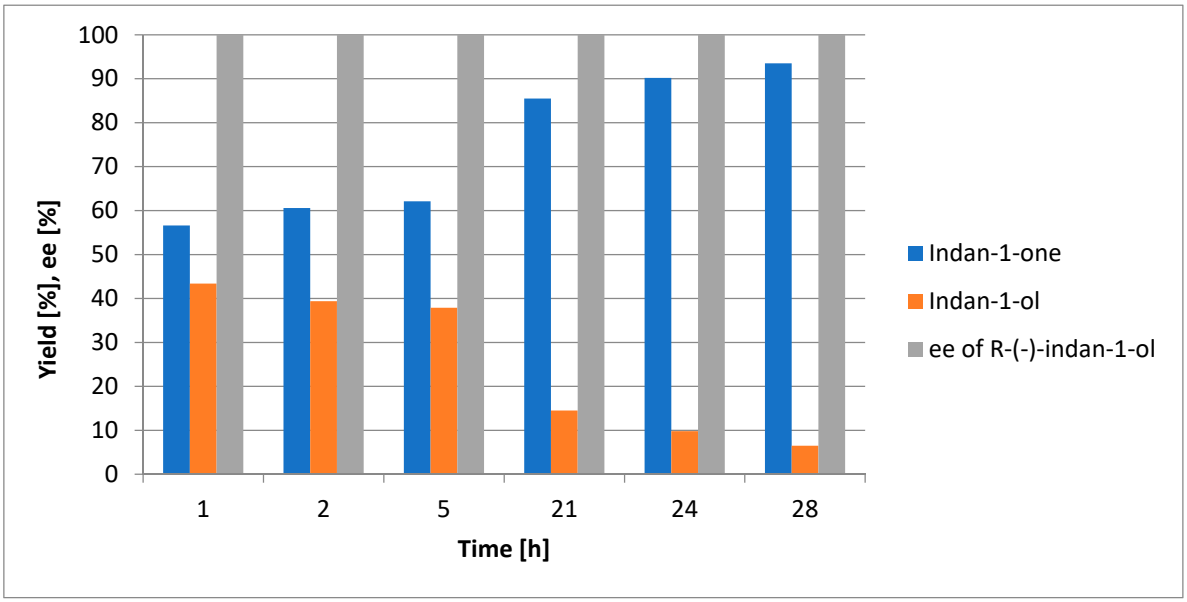


Figure 2. Biotransformation of indan-1-ol by comminuted Jerusalem artichoke.

When analyzing the results of indan-1-ol biotransformation with shredded Jerusalem artichoke pulp, we noticed that during oxidation, the racemic substrate of the *S*-(+)-enantiomer of alcohol was preferred. This reaction was fast, as after one hour over 50% conversion was detected. Only after this *S*-(+)-enantiomer had been depleted did the second of the enantiomers slowly oxidize. This is a very interesting result, considering the literature data available to us, which provides much worse results. Indan-1-ol was oxidized by Uzura [35] in a *Fusarium moniliforme* MS31 culture with a yield of 2.6%. The reaction lasted 35 h. On the other hand, Stampfer [36] published the results of the microbiological oxidation of this compound using the *Rhodococcus ruber* DSM 44541 bacterium. However, after 24 h of the reaction, only 11.3% of the product was obtained.

The Jerusalem artichoke was seldom used as a biocatalyst. Oxidation of (±)-1-phenylethanol, 1-(1-naphthyl)- and 2-(1-naphthyl)ethanol alcohol was presented in a publication by Mironowicz. [12] In the same work the Jerusalem artichoke was also used in the hydrolysis of similar esters, where the oxidation of alcohol was the subsequent reaction. Enzymatic lactonization of three acyclic γ,δ-epoxy esters was revealed in the research by Olejniczak [38]. In turn, Xie et al. [39] described results of 2-chloro-fluorenone biotransformation, where this compound was completely reduced contrary to the Prelog rule, yielding alcohol with an enantiomeric excess of 76% (*R*).

Biotransformations are the first stage of the xenobiotic detoxification process. Many enzymes participate in this process in plants, including cytochrome P450-related enzymes (CYP), alcohol dehydrogenase (ADH), short-chain dehydrogenases/reductases (SDRs), aldo-keto reductases (AKR) and others. Only small ADH families have been found in plants, which function is often unknown. In turn, the SDR superfamily exhibits low sequence similarities. Additionally, the AKR4 subfamily C (AKR4C), a group of aldo-keto reductases found in plants, can also participate in the detoxification of xenobiotics [40].

The enzyme isolated from Jerusalem artichoke, which metabolizes with high efficiency a wide range of xenobiotics, is CYP76B1. This cytochrome P450-containing monooxygenase detoxifies among others several herbicides of the phenylurea class and alkoxycoumarins [41].

The energy metabolism of Jerusalem artichoke tubers is dominated by glycolysis, the tricarboxylic acid cycle, and the mitochondrial electron transport chain, the consequence of which is a high level of NAD synthesis [42]. This cofactor is necessary for all enzymes responsible for alcohol oxidation and ketone reduction. Extremely high conversion of indan-1-ol catalyzed by Jerusalem artichoke tubers

can be the consequence of high levels of cofactor or better substrate specificity of the enzyme present in this vegetable.

3. Experimental

3.1. Biocatalysts

In the present work the following vegetables and fruit were used as a biocatalyst: *Allium ampeloprasum* L.—leek, *Apium graveolens* L.—celeriac, *Beta vulgaris* L.—beet, *Daucus carota* L.—carrot, *Helianthus tuberosus* L.—Jerusalem artichoke, *Pastinaca sativa* L.—parsnip, *Petroselinum crispum* L.—parsley, *Raphanus sativus* L.—radish, *Solanum tuberosum* L.—potato, and *Malus pumila* L.—apple "Gloster". All biocatalysts have been purchased in a local market.

In order to ensure optimal conditions for the enzymes of the intracellular biocatalyst to carry out the reaction, a phosphate buffer with a pH close to the natural juice of the vegetable or fruit was used (Table 3).

Table 3. The pH values of the cell juice of used bioreagents.

Biocatalyst	pH
A. ampeloprasum L. (leek)	6.0
A. graveolens L. var. *rapaceum* (celeriac)	6.2
B. vulgaris L. (beet)	5.9
D. carota L. (carrot),	6.5
H. tuberosus L. (Jerusalem artichoke)	6.9
P. sativa L. (parsnip)	6.5
P. sativum Hoffm: (parsley),	6.5
R. sativus L. (radish)	5.9
S. tuberosum L. (potato)	5.9
M. pumila L.(apple)	4.5

3.2. Duration of Biotransformation

Biotransformations using suspended shredded plant tissues were carried out under non-sterile conditions for up to 48 h. This time was determined on the basis of research performed at our Department. The obtained results allow us to state that the number of bacteria growing at that time has no effect on the course and efficiency of the biotransformation process [43].

3.3. Screening Procedure

The experiments were carried out according to the method worked out by Mączka et al. [44]. Healthy vegetable roots and fruits were comminuted and 20 mL of plant pulp was mixed with 50 mL of 0.1 M phosphate buffer in 300 mL Erlenmayer flasks. Buffer was prepared at the appropriate pH comparable to the pH of cell juice (Table 3). Next, 20 µL of the substrate was dissolved in 0.5 mL acetone and added to the pulp of the biocatalyst. The transformations were performed at room temperature. After 48 h the biotransformed mixtures were extracted with 30 mL of ethyl acetate and dissolved into 2 mL of acetone after evaporation. Under these conditions the substrate in the buffer solution was stable.

Each biotransformation was duplicated. In addition, control samples (buffer + biocatalyst) were prepared out to eliminate the influence of plant-derived metabolites on the interpretation of the results obtained.

The presence of the product was confirmed by analytical TLC, which was performed on silica gel-coated aluminum plates (DC-Alufolien Kieselgel 60 F254, Merck) with a mixture of hexane and acetone in various ratios as the eluent. Compounds were detected by spraying the plates with 20% ethanolic H_2SO_4, which contained 0.1% of anisaldehyde, followed by heating to 120 °C.

The composition of the product mixture was established by GC. This analysis was performed on a CP03380 instrument (Varian, Agilent Technologies, Santa Clara, CA, USA). The temperature program, which was used in GC analysis on the THERMO TR-5 (cross-linked 5% phenyl polisiloxane) capillary column (30 m × 0.32 mm × 1.0 μm), was as follows: Injector 250 °C, detector (FID) 300 °C, column temperature: 100 °C (hold 2 min), 100–200 °C (rate 20 °C/min), 200–300 °C (rate 40 °C/min), 300 °C (hold 1 min). To determine the enantiomeric excess of indan-1-ol, GC analysis was performed using the chiral column Gamma DEX^{TM} 325 (30 m × 0.25 mm × 0.25 μm, Supelco) under the following conditions: Injector 150 °C, detector (FID) 200 °C, column temperature: 110 °C (hold 35 min), 110–200 °C (rate 25 °C/min), 200 °C (hold 1 min).

3.4. Procedure of Preparative Biotransformation

Preparative biotransformations were performed in the same way as screening. Fresh, healthy and undamaged vegetables and fruit were ground after thorough washing. To each of the 10 Erlenmayer flasks with a volume of 300 mL, 20 mL of ground catalyst was metered, and 50 mL of phosphate buffer poured. To each of the samples, 20 μL of the substrate dissolved in 200 μL of acetone, was added. After 48 h the reaction mixtures were extracted with 50 mL of ethyl acetate. The chloroform layer was then carefully collected and dried using anhydrous $MgSO_4$. The resulting solution was filtered and concentrated in a vacuum evaporator.

The products of biotransformation were purified by using preparative column chromatography, which was performed on silica gel (Kieselgel 60, 230–400 mesh ASTM, Merck) with a mixture of hexane and acetone in various ratios as the eluent.

The structure of the obtained product was determined on the basis of physicochemical data **1** compared with the literature data [45]. ^{1}H NMR and ^{13}C NMR spectra were recorded in a DMSO solution on a Bruker Avance DRX 600 MHz.

^{1}H NMR (600 MHz, DMSO): δ: 1.75–1.81 (m, 1H, H-2), 2.34–2.33 (m, 1H, H-2), 2.70–2.73 (m, 1H, H-3), 2.89–2.91 (m, 1H, H-3), 3.41 (s-broad, 1H, OH), 5.05 (t, 1H, H-1, J = 6.0 Hz), 7.18–7.23 (m, 2H, Ar), 7.33–7.39 (m, 2H, Ar), ^{13}C NMR δ: 29.3 (C-2), 35.9 (C-3), 74.8 (C-1), 124.6, 124.9, 126.6, 127.8 (C4,5,6,7), 143.0 (C-8), 146.8 (C-9).

Based on the literature data [46] and the measured rotation, the configuration was assigned to the R isomer: (*R*)-indan-1-ol: $[\alpha]_D^{25}$= −39.3 (*c*1, $CHCl_3$): ($[\alpha]_D^{23}$= −35.2 (*c*1.05, $CHCl_3$) lit [46]).

3.5. Investigation of Biotransformation over Time

In order to verify the course of the indan-1-ol biotransformation over time, the reaction was terminated after 1, 2, 5, 21, 24, 28 h. The enzymatic system of the Jerusalem artichoke was used as the biocatalyst.

4. Conclusions

Indanol enantiomers can find versatile use as chirons in the organic synthesis of other useful compounds. In this work, we carried out biotransformation using plant catalysts to obtain indanol isomers with a high enantiomeric excess. We tested the ability of our catalysts to perform both stereoselective reduction and oxidation. Reduction of indan-1-one was found catalyzed by only six of the eleven plant catalysts under analysis. The reaction was highly stereoselective, allowing the pure *S*-(+)-indanol enantiomer to be obtained, but conversion was low, i.e., up to 8.5% in the case of *D. carota*, for instance. For this reason, we decided to study the ability of plant catalysts to perform a stereoselective oxidation of racemic indan-1-ol. All catalysts were able to carry out this reaction. The conversion rate was higher than in the case of reduction; however, in most cases transformation was at low stereoselectivity, except for the Jerusalem artichoke, in which conversion reached 99.5 and the pure *R*-(–)-enantiomer remained in the reaction mixture. Investigation of this biotransformation over time has enabled to establish that as early as after one hour of transformation, the *S*-(+) alcohol enantiomer totally reacts, leaving the second (*R*-(–)-) enantiomer intact.

Author Contributions: W.M. conceived, designed the experiments and analyzed the data, W.M. and K.W. performed the experiments, W.M., K.W. and M.G. wrote the paper, M.G. analyzed the NMR spectrum of products, R.G.—confirmed botanical compatibility.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ballard, A.; Narduolo, S.; Ahmad, H.O.; Cosgrove, D.A.; Leach, A.G.; Buurma, N.J. The problem of racemization in drug discovery and tools to predict it. *Expert Opin. Drug Discov.* **2019**. [CrossRef]
2. Talsi, E.P.; Bryliakov, K.P. Autoamplification-enhanced oxidative kinetic resolution of sec-alcohols and alkyl mandelates, and its kinetic model. *ChemCatChem* **2018**, *10*, 2693–2699. [CrossRef]
3. Hashimoto, T.; Shimazaki, Y.; Omatsu, Y.; Maruoka, K. Indanol-based chiral organoiodine catalysts for enantioselective hydrative dearomatization. *Angew. Chem. Int. Ed.* **2018**, *57*, 7200–7204. [CrossRef] [PubMed]
4. Ghanem, A.; Ahmed, M.; Ishii, H.; Ikegami, T. Immobilized β-cyclodextrin-based silica vs polymer monoliths for chiral nano liquid chromatographic separation of racemates. *Talanta* **2015**, *132*, 301–314. [CrossRef]
5. Garbe, M.; Wei, Z.; Tannert, B.; Spannenberg, A.; Jiao, H.; Bachmann, S.; Scalone, M.; Junge, K.; Beller, M. Enantioselective hydrogenation of ketones using different metal complexes with a chiral PNP pincer ligand. *Adv. Synth. Catal.* **2019**, *361*, 1913–1920. [CrossRef]
6. Kumar, R.; Banoth, L.; Banerjee, U.C.; Kaura, J. Enantiomeric separation of pharmaceutically important drug intermediates using a metagenomic lipase and optimization of its large scale production. *Int. J. Biol. Macromol.* **2017**, *95*, 995–1003. [CrossRef]
7. Sun, H.; Zhang, H.; Ang, E.L.; Zhao, H. Biocatalysis for the synthesis of pharmaceuticals and pharmaceutical intermediates. *Bioorg. Med. Chem. Lett.* **2018**, *26*, 1275–1284. [CrossRef]
8. Mączka, W.K.; Mironowicz, A. Enantioselective hydrolysis of 1-aryl ethyl acetates and reduction of aryl methyl ketones using carrot, celeriac and horseradish enzyme systems. *Tetrahedron Asymmetry* **2002**, *13*, 2299–2302. [CrossRef]
9. Mączka, W.K.; Mironowicz, A. Enantioselective reduction of bromo- and methoxy-acetophenone derivatives using carrot and celeriac enzymatic system. *Tetrahedron Asymmetry* **2004**, *15*, 1965–1967. [CrossRef]
10. Meshram, S.H.; Ramesh, T.; Nanubolu, J.B.; Srivastava, A.K.; Adari, B.R.; Sahu, N. Green synthesis of enantiopure quinoxaline alcohols using *Daucus carota*. *Chirality* **2019**, *31*, 312–320. [CrossRef]
11. Kazici, H.C.; Bayraktar, E.; Mehmetoglu, Ü. Production of precursors for anti-Alzheimer drugs: Asymmetric bioreduction in a packed-bed bioreactor using immobilized *D. carota* cells. *Prep. Biochem. Biotechnol.* **2017**, *47*, 67–73. [CrossRef] [PubMed]
12. Mironowicz, A. Biotransformations of racemic acetates by potato and topinambur tubers. *Phytochemistry* **1998**, *47*, 1531–1534. [CrossRef]
13. Itoh, K.; Nakamura, K.; Utsukihara, T.; Sakamaki, H.; Horiuchi, A.C. Stereoselective oxidation of racemic 1-arylethanols by basil cultured cells of *Ocimum basilicum* cv. *purpurascens. Biotechnol. Lett.* **2008**, *30*, 951–954. [CrossRef] [PubMed]
14. Andrade, L.H.; Utsunomiya, R.S.; Omori, A.T.; Porto, A.L.M.; Comasseto, J.V. Edible catalysts for clean chemical reactions: Bioreduction of aromatic ketones and biooxidation of secondary alcohols using plants. *J. Mol. Catal. B Enzym.* **2006**, *38*, 84–90. [CrossRef]
15. Utsukihara, T.; Horiuchi, A.C. Production of chiral aromatic alcohol by acetophenone and 1-arylethanol derivatives using vegetables. *Indian J. Chem.* **2019**, *58B*, 69–74.
16. Nasário, F.D.; Cazetta, T.; Moran, P.J.S.; Rodrigues, J.A.R. Deracemization of 1-phenylethanol via tandem biocatalytic oxidation and reduction. *Tetrahedron Asymmetry* **2016**, *27*, 404–409. [CrossRef]
17. Liu, J.; Wu, S.; Li, Z. Recent advances in enzymatic oxidation of alcohols. *Curr. Opin. Chem. Biol.* **2018**, *43*, 77–86. [CrossRef]
18. Carvalho da Silva, R.A.; de Mesquita, B.M.; de Farias, I.F.; Garcia do Nascimento, P.G.; Gomes de Lemos, T.L.; Queiroz Monte, F.J. Enzymatic chemical transformations of aldehydes, ketones, esters and alcohols using plant fragments as the only biocatalyst: *Ximenia americana* grains. *Mol. Catal.* **2018**, *445*, 187–194. [CrossRef]
19. Aldabalde, V.; Arcia, P.; Gonzalez, A.; Gonzalez, D. Enzymatic synthesis of chiral heteroaryl alcohols using plant fragments as the only biocatalyst and reducing agent. *Green Chem. Lett. Rev.* **2007**, *1*, 25–30. [CrossRef]

20. Bennamane, M.; Zeror, S.; Aribi-Zouioueche, L. Asymmetric Reduction of Ketones by biocatalysis using clementine mandarin (*Citrus reticulata*) fruit grown in Annaba or by ruthenium catalysis for access to both enantiomers. *Chirality* **2015**, *27*, 205–210. [CrossRef]
21. Bennamane, M.; Razi, S.; Zeror, S.; Aribi-Zouioueche, L. Preparation of chiral phenylethanols using various vegetables grown in Algeria. *Biocatal. Agric. Biotechnol.* **2018**, *14*, 52–56. [CrossRef]
22. Cordell, G.A.; Lemos, T.L.G.; Monte, F.J.Q.; de Mattos, M.C. Vegetables as chemical reagents. *J. Nat. Prod.* **2007**, *70*, 478–492. [CrossRef] [PubMed]
23. Machado, L.L.; Monte, F.J.Q.; de Oliveira, M.C.F.; de Mattos, M.C.; Lemos, T.L.G.; Gotor-Fernández, V.; de Gonzalo, G.; Gotor, V. Bioreduction of aromatic aldehydes and ketones by fruits'barks of *Passiflora edulis*. *J. Mol. Catal. B Enzym.* **2008**, *55*, 130–133. [CrossRef]
24. Yadav, J.S.; Nanda, S.; Thirupathi Reddy, P.; Bhaskar Rao, A. Efficient enantioselective reduction of ketones with *Daucus carota* root. *J. Org. Chem.* **2002**, *67*, 3900–3903. [CrossRef] [PubMed]
25. Pavokovic, D.; Buda, R.; Andrašec, F.; Roje, M.; Cvjetko Bubalo, M.; Radojcic Redovnikovic, I. Plant-mediated asymmetric reduction of 1-(3,4-dimethylphenyl)ethanone. *Tetrahedron Asymmetry* **2017**, *28*, 730–733. [CrossRef]
26. Catallo, W.J.; Shupe, T.F.; Eberhardt, T.L. Hydrothermal processing of biomass from invasive aquatic plants. *Biomass Bioenergy* **2008**, *32*, 140–145. [CrossRef]
27. Lawton, R.O.; Alexander, L.D.; Setzer, W.N.; Byler, K.G. Floral essential oil of *Guettarda poasana* inhibits yeast growth. *Biotropica* **1993**, *25*, 483–486. [CrossRef]
28. Fushimi, K.; Horikawa, M.; Suzuki, K.; Sekiya, A.; Kanno, S.; Shimura, S.; Kawagishi, H. Applanatines A to E from the culture broth of *Ganoderma applanatum*. *Tetrahedron* **2010**, *66*, 9332–9335. [CrossRef]
29. Gallou, I.; Senanayake, C.H. *cis*-1-Amino-2-indanol in drug design and applications to asymmetric processes. *Chem. Rev.* **2006**, *106*, 2843–2874. [CrossRef]
30. Calitz, C.; Gouws, C.; Viljoen, J.; Steenekamp, J.; Wiesner, L.; Abay, E.; Hamman, J. Herb-drug pharmacokinetic interactions: Transport and metabolism of Indinavir in the presence of selected herbal products. *Molecules* **2015**, *20*, 22113–22127. [CrossRef]
31. Lourenco, N.M.T.; Barreiros, S.; Afonso, C.A.M. Enzymatic resolution of Indinavir precursor in ionic liquids with reuse of biocatalyst and media by product sublimation. *Green Chem.* **2007**, *9*, 734–736. [CrossRef]
32. Kameyama, M.; Siqueira, F.A.; Garcia-Mijares, M.; Silva, L.F., Jr.; Silva, M.T.A. Indatraline: Synthesis and effect on the motor activity of Wistar rats. *Molecules* **2011**, *16*, 9421–9438. [CrossRef] [PubMed]
33. Xu, R.; Wang, K.; Rizzi, J.P.; Huang, H.; Grina, J.A.; Schlachter, S.T.; Wang, B.; Wehn, P.M.; Yang, H.; Dixon, D.D.; et al. 3-[(1*S*,2*S*,3*R*)-2,3-Difluoro-1-hydroxy-7-methylsulfonylindan-4-yl]oxy-5-fluorobenzonitrile (PT2977), a hypoxia-inducible factor 2α (HIF-2α) inhibitor for the treatment of clear cell Renal cell carcinoma. *J. Med. Chem.* **2019**, *62*, 6876–6893. [CrossRef] [PubMed]
34. Nagaki, M.; Soma, N.; Ono, K.; Yamanouchi, K.; Tsujiguchi, T.; Kawakami, J.; Chounan, Y. Biotransformation of indanol, fluorenol and their analogs using tissue-cultured cells and their antimicrobial activity. *Trans. Mater. Res. Soc. Jpn.* **2019**, *44*, 29–33. [CrossRef]
35. Uzura, A.; Katsuragi, T.; Tani, Y. Conversion of various aromatic compounds by resting cells of *Fusarium moniliforme* strain MS31. *J. Biosci. Bioeng.* **2001**, *92*, 381–384. [CrossRef]
36. Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W. Biocatalytic asymmetric hydrogen transfer employing *Rhodococcus ruber* DSM 44541. *J. Org. Chem.* **2003**, *68*, 402–406. [CrossRef]
37. Bouzemi, N.; Aribi-Zouioueche, L.; Fiaud, J.C. Combined lipase-catalyzed resolution/Mitsunobu esterification for the production of enantiomerically enriched arylalkyl carbinols. *Tetrahedron Asymm* **2006**, *17*, 797–800. [CrossRef]
38. Olejniczak, T.; Mironowicz, A.; Wawrzeńczyk, C. Lactones 12. Enzymatic lactonization of γ,δ-epoxy esters by the apple fruit and Jerusalem artichoke bulb. *Bioorg. Chem.* **2003**, *31*, 199–205. [CrossRef]
39. Xie, B.; Yang, J.; Yang, Q.; Yuan, W. Enantioselective reduction of fluorenones in surfactant-aqueous solution by fruits and vegetables. *J. Mol. Catal. B Enzym.* **2009**, *61*, 284–288. [CrossRef]
40. Bártíková, H.; Skálová, L.; Stuchlíková, L.; Vokřál, I.; Vaněk, T.; Podlipná, R. Xenobiotic-metabolizing enzymes in plants and their role in uptake and biotransformation of veterinary drugs in the environment. *Drug Metab. Rev.* **2015**, *47*, 374–387.

41. Robineau, T.; Batard, Y.; Nedelkina, S.; Cabello-Hurtado, F.; LeRet, M.; Sorokine, O.; Didierjean, L.; Werck-Reichhart, D. The chemically inducible plant cytochromeP450 CYP76B1 actively metabolizes phenylureas and other xeno-biotics. *Plant Physiol.* **1998**, *118*, 1049–1056. [CrossRef] [PubMed]
42. Di Martino, C.; Pallotta, M.L. Mitochondria-localized NAD biosynthesis by nicotinamide mononucleotide adenylyltransferase in Jerusalem artichoke (*Helianthus tuberosus* L.) heterotrophic tissues. *Planta* **2011**, *234*, 657–670. [CrossRef] [PubMed]
43. Mironowicz, A. Wykorzystanie komórek roślinnych do biotransformacji ksenobiotycznych, strukturalnie zróżnicowanych związków chemicznych. In *Zeszyty Naukowe Akademii Rolniczej we Wrocławiu Nr 354 Rozprawy CL XXII*; Wydawnictwo Akademii Rolniczej we Wrocławiu: Wrocław, Poland, 1999.
44. Mączka, W.; Sołtysik, D.; Wińska, K.; Grabarczyk, M.; Szumny, A. Plant-mediated biotransformations of *S*(+)- and *R*(−)-carvones. *Appl. Sci.* **2018**, *8*, 2605.
45. Rebelo, S.L.H.; Simoes, M.M.Q.; Neves, M.G.P.M.S.; Silva, A.M.S.; Tagliatesta, P.; Cavaleiro, J.A.S. Oxidation of bicyclic arenes with hydrogen peroxide catalysed by Mn(III) porphyrins. *J. Mol. Catal. A Chem.* **2003**, *232*, 135–142. [CrossRef]
46. Lie, F.; Chen, Y.; Wang, Z.; Li, Z. Enantioselective benzylic hydroxylation of indan and tetralin with *Pseudomonas monteilii* TA-5. *Tetrahedron Asymmetry* **2009**, *20*, 1206–1211. [CrossRef]