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Chemoenzymatic Cascade Reaction for the Valorization of the Lignin Depolymerization Product G–C2-Dioxolane Phenol

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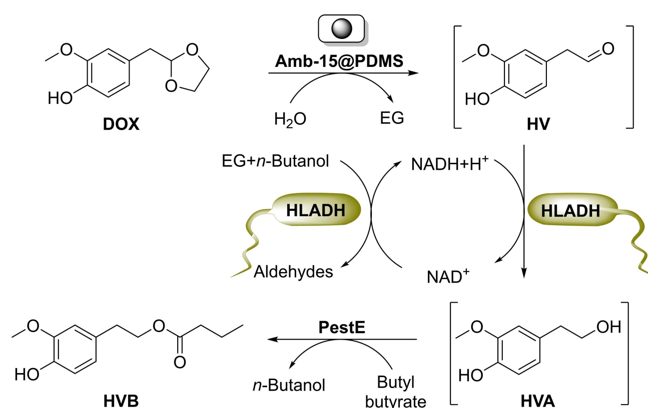
Combining solid acid catalysts with enzyme reactions in aqueous environments is challenging because either very acidic conditions inactivate the enzymes, or the solid acid catalyst is neutralized. In this study, Amberlyst-15 encapsulated in polydimethylsiloxane (Amb-15@PDMS) is used to deprotect the lignin depolymerization product G–C2 dioxolane phenol in a buffered system at pH 6.0. This reaction is directly coupled with the biocatalytic reduction of the released homovanillin to homovanillyl alcohol by recombinant horse liver alcohol dehydrogenase, which is subsequently acylated by the promiscuous acyltransferase/hydrolase PestE_I208A_L209F_N288A in a one-pot system. The deprotection catalyzed with Amb-15@PDMS attains up to 97% conversion. Overall, this cascade enables conversions of up to 57%.

Introduction

Valorization of lignocellulose-derived lignin can provide a sustainable route for the production of phenolic compounds.[1] However, in conventional pulp production, lignin extraction leads to an irreversibly altered complex structure that makes it impossible to produce defined depolymerization products.[2] The "lignin first" approach aims to extract and depolymerize lignin from lignocellulose without compromising the utilization of cellulose and hemicellulose.[2,3] Diol-assisted lignocellulose fractionation follows the lignin-first approach and prevents the repolymerization of reactive species formed during acid-catalyzed depolymerization by the formation of diol-based lignin mono- and oligomer acetals.[3–7] Diol-assisted acidolysis of the β-*O*-4′-bond in lignin of softwoods such as pine, cedar, or spruce with ethylene glycol leads to the formation of an acetal derived from the lignin subunit G (G–C2-dioxolane phenol, DOX; Scheme 1).[5] Recently, the synthesis of various dopamine-based biologically active molecules was described starting with DOX.[8] An important step of the described synthesis is the catalytic hydration of DOX to homovanillyl alcohol (HVA) using



Scheme 1. Chemoenzymatic cascade for the synthesis of homovanillyl butyrate from G–C2-dioxolane phenol (DOX). Amb-15@PDMS catalyzes the deprotection of DOX (accessible from the diol (EG)-assisted acidolysis of softwood lignin) to HV.[5] HV is reduced to HVA by lyophilized *E. coli* whole cells containing HLADH. HLADH recycles NADH using ethylene glycol (EG) and *n*-butanol released during the other reaction steps. PestE_I208A_L209F_N288A acylates HVA to HVB.

Ru/Al_2O_3, H_2 under high pressure and elevated temperatures. Additionally, the deprotection of a phenol-methylated version of DOX was achieved in situ for use in the corresponding Pictet–Spengler cyclization.

In this work, we aimed to utilize DOX to produce homovanillyl butyrate (HVB), a lipophilized derivative of HVA, with antioxidant properties.[9] HVA is an antioxidant with protective effects on cardiovascular diseases and a metabolite of hydroxytyrosol.[10,11] A chemoenzymatic cascade involving deacetalization, reduction, and acylation steps was considered for the conversion of DOX to homovanillyl butyrate (Scheme 1). In contrast to previous studies, HVA should be synthesized without noble metal catalysts and under mild reaction conditions by enzymatic reduction. However, this requires deacetalization of DOX to homovanillin (HV), which is known to be labile

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under acidic conditions typically used for acetal deprotection.[12,13] Furthermore, in organic solvents the reaction comes into equilibrium with the reverse reaction, resulting in incomplete deprotection. Therefore, acetone is usually added to shift the equilibrium for deprotection of this type of compounds.[14–16] In contrast, we deprotected DOX in water, avoiding the addition of acetone to shift the reaction equilibrium. Direct coupling of the deacetalization of DOX with the reduction of the HV formed by horse liver alcohol dehydrogenase (HLADH), recombinantly produced in *E. coli*, prevents the accumulation and condensation of HV. To further shift the equilibrium of the HLADH reaction, we used an enzymatic acyltransferase reaction, which was carried out by the promiscuous acyltransferase/hydrolase from *Pyrobaculum calidifontis* VA1 (PestE).[17] The variant PestE_I208A_L209F_N288A was previously optimized by us for hydroxytyrosol acetylation in an aqueous/organic two-phase system and applied in a cascade reaction to obtain hydroxytyrosol acetate from olive mill wastewater.[18,19] In the present study, we found that PestE_I208A_L209F_N288A also acylated the structurally related homovanillyl alcohol. Apart from shifting the equilibrium of the HLADH reaction, lipophilization of homovanillyl alcohol in homology to hydroxytyrosol could enhance the membrane permeability of this antioxidant.[20,21] However, since strongly acidic conditions required for the deacetalization of the G–C2-dioxolane phenol are incompatible with the enzymatic reactions, a compartmentalization strategy was used to establish a one-pot reaction. For this purpose, the polymeric solid acid catalyst Amberlyst 15 (Merck KGaA, Darmstadt, Germany), which contains sulfonic acid residues, was encapsulated in the hydrophobic polydimethylsiloxane (PDMS) polymer, resulting in Amb-15@PDMS. The combination of enzyme reactions with solid acid catalysts in an aqueous one-pot reactions has so far been little explored. The only known one-pot cascade combining a solid acid catalyst and an enzyme could not be performed in buffered solution as this resulted in a rapid deactivation of the enzyme under the harsh reaction conditions.[22] Here we report on the development of a catalytic cascade that starts with Amb-15@PDMS as solid acid catalysis in buffered water demonstrating its compatibility as a suitable environment for enzymes.

Results and Discussion

The instability of phenolic compounds at basic pH is well known.[23,24] Therefore, pH 6.0 was chosen to perform the cascade reaction. A pH screening showed that both enzymes tolerated this pH, but PestE_I208A_L209F_N288A was more active in 50 mM sodium citrate buffer, whereas HLADH was more active in sodium phosphate buffer (see the Supporting Information, Figures S1 and S3). A 1:1 mixture of both buffers was found to be beneficial for both enzymes. While Amberlyst-15 is water stable and has been used in various aqueous systems,[25–28] it is not compatible with enzyme reactions because buffer salts either completely neutralize the acidic functions of Amberlyst-15 (Table S2, entry 10) or acidification occurs, when buffer capacity is exceeded, which inactivate the enzymes. To protect the solid acid catalyst, the Amberlyst-15 beads were encapsulated in PDMS, resulting in Amb-15@PDMS. PDMS retains buffer salts but allows organic compounds to enter.[29–31] Therefore, proton transfer by buffer salts and hydronium ions does not rapidly inactivate the solid acid catalysts, although PDMS has some water permeability, enabling deacetalization.[32] With ten Amb-15@PDMS punchings it was possible to reach 97% conversion in 24 h at 20 °C without addition of the enzymes for the cascade (Table S1, entry 10).

However, due to the large differences in deprotection activity (Table S2), the conversions achieved in the initial cascade reactions varied widely (Table S1). Nevertheless, with careful selection of Amb-15@PDMS beads, where the catalyst is located in the center of the punching, DOX deacetalization efficiencies of up to 97% were achieved in the cascade reaction (Table 1; entry 1). In addition, Amb-15@PDMS can be recycled without further regeneration, as demonstrated for single Amb-15@PDMS beads (Table S2). Interestingly, beads that showed low activity when first used showed no activity when reused, indicating that the beads were deactivated during the first reaction cycle, possibly due to the disintegration of the beads during the first use and neutralization of the acid functions by buffer salts (Figure S4; for example, beads 5 and 9). Apart from bead 6, similar conversions were achieved with reused beads (Table S2). This demonstrates the robustness of the newly developed Amb-15@PDMS catalyst making them a promising candidate for combining solid acid catalysts with various enzymatic reactions. From a practical point of view, washing Amb-15@PDMS twice with ethyl acetate was sufficient to efficiently extract the contained organic compounds. A third washing step performed in initial experiments did not contain DOX, HV, HVA or HVB, demonstrating efficient recovery of these organic compounds from the reaction system. Since DOX and HVB are mainly recovered from the Amb-15@PDMS beads, while HV and HVA are mainly recovered from the aqueous phase (data not shown), the separation of Amb-15@PDMS beads could facilitate the downstream processing of HVB. To optimize the extraction of HVB, the diameter of the Amb-15@PDMS beads could also be changed. However, the reactivity

Table 1. Chemoenzymatic cascade reactions for the synthesis of HVB.[a]

Entry	HLADH	PestE	DOX	HV	HVA	HVB
1	OD_{600} 500	20 µg	3 ± 1%	3 ± 2%	37 ± 1%	57 ± 0%
2	OD_{600} 100	20 µg	14 ± 6%	50 ± 2%	13 ± 3%	23 ± 2%
3	OD_{600} 15	20 µg	13 ± 7%	75 ± 7%	4 ± 0%	8 ± 0%
4	–	–	3 ± 0%	97 ± 0%	n.d.	n.d.

[a] Reaction conditions: 5 mM G–C2 dioxolane phenol, 7 mg Amb-15@PDMS (containing approximately 1.4 mg Amb-15; 10 beads), 20% (v/v) butyl butyrate, and purified PestE_I208A_L209F_N288 A were added. The 100-µL-scale reaction in sodium phosphate/citrate buffer (25 mM each; pH 6.0) was performed at 20 °C (1000 rpm) for 24 h. The conversions are relative to the recovered molecules, the recovery rate was about 80%. HLADH was expressed in *E. coli* whole cells and used as a lyophilizate. All reactions were extracted twice with 200 µL ethyl acetate and Amb-15@PDMS was also washed twice. Values shown are means of duplicates. OD_{600} was measured before lyophilization and the amount of lyophilisate added was adjusted accordingly. Experiments were performed with beads where accurate Amb-15@PDMS punching was double checked.

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and stability of the beads must be taken into account when doing so.

Unfortunately, the presence of Amb-15@PDMS was not compatible to the commercial HLADH used in the initial experiments (data not shown), which may be attributed to its immobilization on the PDMS surface.[33,34] We found that the addition of 2 mg mL^{-1} bovine serum albumin could partially prevent immobilization and inactivation. Also, the acyl donor ethyl acetate used to promote the subsequent acyltransferase reaction is greatly reducing HLADH activity (Figure S2) and thus a compartmentalization appeared to be a more promising strategy. Therefore, recombinantly expressed HLADH in lyophilized *E. coli* BL21 whole cells was used. The use of whole cells had the unexpected advantage that the endogenous enzymes also showed some activity in reducing HV to HVA, as seen in a control reaction with empty vector-containing *E. coli* BL21 whole cells (Table S1; entry 1). To find an acyl donor that inhibits HLADH less strongly, is less volatile, and is accepted by PestE, phenyl acetate and butyl butyrate were investigated. Both acyl donors were selected because they are less polar and water-soluble than ethyl acetate, similar to the established co-solvent *n*-hexane.[35] In fact, phenyl acetate and butyl butyrate inhibit HLADH less than ethyl acetate, but butyl butyrate was selected because it can be produced from sustainable resources.[36] Nevertheless, the activity of HLADH remained low, and large amounts of whole-cell lyophilizate were required to achieve 97% conversion of the HV produced to HVA (Table 1). Further studies could apply enzyme engineering to HLADH or search for an ADH with higher activity toward HVA to reduce the amount of ADH used.

Promiscuous acyltransferases/hydrolases are capable of catalyzing transesterification reactions, usually carried out in organic solvents, in water. The robust promiscuous acyltransferase/hydrolase PestE_I208A_L209F_N288A is not inactivated by Amb-15@PDMS and can be added as an isolated enzyme from (heat-treated) lysate or from lyophilized *E. coli* whole cells (Table S1). In the absence of PestE_I208A_L209F_N288A, only trace amounts of HVB were formed, indicating that HVB formation originates from the acyltransferase. Conversions of up to 61 $\pm$ 0% were obtained for the acylation step, although solid acid catalysts are in principle capable of hydrolyzing esters.[37,38] Moreover, complete conversions with butyl butyrate as the acyl donor are not expected because the butanol released during the acyl transfer and hydrolysis of the acyl donor favors the reverse reaction. Conversions of 68 $\pm$ 1% were achieved when 5 mM HVA was converted by PestE_I208A_L209F_N288A in the presence of ten Amb-15@PDMS beads, indicating that the 61% conversion achieved in the cascade is close to the maximum conversions expected for this system. To achieve good conversions with acyl donors from aliphatic esters or poor acyltransferase substrates, a large excess of acyl donor is usually added to form a second phase, shifting the equilibrium and preventing hydrolysis of the product by extraction.[39] Therefore, 20% (v/v) butyl butyrate was added to the reaction. However, in the system described, the liquid organic phase was rapidly absorbed by the Amb-15@PDMS beads, resulting in a two-phase system consisting of an organic-solid phase and an aqueous-liquid phase. Increasing the amount of butyl butyrate to 50% (v/v) did not increase the conversion of the acyl transfer step (Table S1, entry 6), indicating that 20% acyl donor is already sufficient to achieve maximal conversions.

The use of purified PestE_I208A_L209F_N288A has shown that the direct coupling of Amb-15@PDMS with enzymes is possible. Furthermore, using HLADH as an example, we have shown that even challenging enzymes can be combined with Amb-15@PDMS when used as recombinantly expressed enzymes in whole cells. Most importantly, this chemoenzymatic cascade reaction showed a potential valorization strategy for the lignin depolymerization product DOX and potentially acetal compounds originating from the H and S subunits of lignin.

Conclusion

A cascade chemoenzymatic reaction was applied for the deacetalization, reduction, and acylation of the lignin depolymerization product G–C2 dioxolane phenol, achieving up to 57% conversion into HVB using Amb-15@PDMS, *E. coli* BL21 whole cells containing HLADH, and PestE_I208A_L209F_N288A. With deacetalization and transesterification, two reactions that are typically incompatible with buffered aqueous systems were combined in a cascade reaction under mild reaction conditions. Amb-15@PDMS was developed as a solid acid catalyst that can work in buffered aqueous solution and is compatible with enzymatic reactions. Therefore, Amb-15@PDMS can be a pioneer for coupling solid acid catalysts and enzymatic reactions under mild aqueous conditions. The combination of Amb-15@PDMS with the labile HLADH was demonstrated, even if the enzyme had to be protected in whole cells. In contrast, PestE_I208A_L209F_N288A could be used as a free protein, highlighting the robustness and compatibility of the enzyme in cascade reactions.

Experimental Section

Enzyme preparation

Chemically competent *E. coli* BL21 (DE3) cells were transformed with the expression vectors pET21a_PestE_I208A_L209F_N288A or pET28a_HLADH by heat shock and plated on LB agar containing 100 μg mL^{-1} ampicillin (Amp) or 50 μg mL^{-1} kanamycin (Kan), respectively. 4 mL Lysogeny broth (LB) pre-cultures containing Amp or Kan were inoculated and incubated overnight (37 °C, 140 rpm). LB medium (50–600 mL) was inoculated with 1% (v/v) of the pre-culture and incubated (37 °C, 140 rpm) until it reached OD_{600} of 0.6. Protein expression was induced by the addition of isopropyl-β-D-thiogalactopyranoside (IPTG) to a final concentration of 0.5 mM and incubated overnight (~20 h) at 20 °C and 140 rpm. Cells were harvested by centrifugation at 10,000 *g* and 4 °C for 5 min.

For the preparation of HLADH, *E. coli* cells were resuspended in 4 mL reaction buffer (50 mM sodium phosphate, 50 mM sodium citrate buffer, pH 6.0) per gram of cells to produce whole cells, and OD_{600} was measured. The resuspension was lyophilized for the

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cascade reaction. Preparation of whole cells containing the empty pET28a vector was performed accordingly.

For the purification of PestE_I208A_L209F_N288A, cell pellets were resuspended with 4 mL lysis buffer (10 mM imidazole, 50 mM potassium phosphate, 300 mM sodium chloride, pH 8.0) per gram of cells. The cell solutions were lysed by sonification on ice (two cycles of 5 min sonication (50% intensity, 50% pulsed cycle)) using a SONOPULS HD 2070 (BANDELIN Electronic GmbH & Co. KG, Berlin, Germany). After centrifugation at 10,000 *g* and 4 °C for 30 min. For purification, the crude lysates were applied to 1.5 mL Roti®Garose-His/Ni Beads (Carl Roth, Karlsruhe, Germany). The resins were washed with 15 mL washing buffer (20 mM imidazole, 50 mM sodium phosphate, 300 mM sodium chloride, pH 8.0) before target proteins were eluted with elution buffer (250 mM imidazole, 50 mM sodium phosphate, 300 mM sodium chloride, pH 8.0). Elution fractions were treated at 80 °C for 20 min (500 rpm), centrifuged (17,000 *g*, 4 °C for 5 min), and the supernatant transferred to the storage buffer (50 mM sodium phosphate, pH 7.5) using PD-10 desalting columns (GE Healthcare, UK). Protein concentrations were determined at 280 nm using a NanoDrop™ 1000 spectrophotometer (ThermoFisher, Germany).

Lyophilization, when appropriate, was performed overnight in a Christ™ Alpha 1–2 lyophilizer (Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany).

Deprotection with Amb-15@PDMS

Ten Amb-15@PDMS (approximately 7 mg containing 1.4 mg Amb-15), 10 μL DOX solution (from a 50 mM stock in butyl butyrate; 5 mM final concentration), 10 μL butyl butyrate, and 80 μL sodium phosphate/citrate buffer (25 mM each; pH 6.0) were added to a 1.5-mL GC vial and incubated for 24 h at 20 °C (1000 rpm). The aqueous phase was separated and extracted twice with 200 μL ethyl acetate. The beads were washed twice with 200 μL ethyl acetate (10 min, 20 °C, 1000 rpm). The ethyl acetate phases were combined and dried with anhydrous sodium sulfate before gas chromatography (GC) analysis.

Cascade reactions

Reactions were performed according to the following protocol unless stated differently. Ten Amb-15@PDMS (approximately 7 mg containing 1.4 mg Amb-15), 2.5 μL DOX solution (from a 200 mM stock in butyl butyrate; 5 mM final concentration), 17.5 μL butyl butyrate, and 80 μL sodium phosphate/citrate buffer (25 mM each; pH 6.0) with 20 μg PestE_I208A_L209F_N288A and lyophilized *E. coli* BL21 (DE3) containing HLADH (final $OD_{600}=500$ calculated on the basis of cell density before lyophilization) were added to a 1.5-mL GC vial. The reaction was incubated for 24 h at 20 °C (1000 rpm), the aqueous phase was separated and extracted twice with 200 μL ethyl acetate. The beads were washed twice with 200 μL ethyl acetate (15 min, 20 °C, 1000 rpm). The ethyl acetate phases were combined and dried with anhydrous sodium sulfate before gas chromatography (GC) analysis.

GC-FID analytics

Analysis was performed with a GC-FID (GC-2010, Shimadzu, Kyoto, Japan) equipped with a ZB 5MSi column (25.0 m × 0.25 mm, 0.25 μm film thickness, Phenomenex, Torrence, California, USA). Injector and detector temperature was 250 °C, and 1 μL sample was injected. The column temperature was held at 160 °C for 3.0 min, increased to 190 °C with 14 °C min^{-1}, and held 4.9 min. Total time: 10 min. Retention times: DOX: 6.75 min, HV: 3.97 min; HVA: 4.65 min; HVB: 8.67 min.

Preparation of Amb-15@PDMS

The commercial PDMS Sylgard® 184 (Merck KGaA, Darmstadt, Germany) was prepared by adding 1 part of hardener to 10 parts of PDMS base (total volume: 12 mL). After mixing the reagents, the mixture was added to 100 mg dry Amberlyst-15 (Sigma-Aldrich) in a Petri dish. The dish was inverted several times and quickly inverted back to ensure that the Amberlyst-15 was completely surrounded by PDMS. The reaction product cured overnight at room temperature and for an additional 4 h 60 °C. The Amb-15@PDMS beads were cut using a 1.5 mm diameter biopsy punch.

Synthesis of G-C2-dioxolane phenol

The G–C2-dioxolane phenol can be isolated form the reaction mixture of diol (EG)-assisted softwood lignin acidolysis[7] or reaction mixture under a diol (EG)-assisted lignin-first approach.[5] Separation of G–C2-dioxolane phenol via column chromatography from beech ethanosolv lignin has been demonstrated in our previous study.[4] In this study, we used C2-dioxolane phenol synthesized via a modified literature procedure.[40] Under N_2 atmosphere, 3.25 g *N*-bromosuccinimide (18.5 mmol, NBS) and 4.75 g silver trifluoromethanesulfonate (18.5 mmol) were dispersed in 30 mL dichloromethane and 15 mL ethylene glycol. Subsequently, 2.5 mL (18.5 mmol) 4-vinyl guaiacol was added dropwise to the mixture and allowed to stir for 30 min. The reaction was quenched by adding 10 mL H_2O, 10 mL saturated $NaHCO_3$ solution, and 40 mL saturated $Na_2S_2O_3$ solution. The mixture was then extracted with dichloromethane (20 mL × 3) and purified by column chromatography (ethyl acetate/pentane 5–30%). G-C2-dioxolane was obtained as yellowish oil (0.01 mol, 54% yield, ^{1}H NMR purity: 95%). The obtained data are consistent with literature. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=6.85$ (d, $J=8.0$ Hz, 1H), 6.81–6.73 (m, 2H), 5.52 (s, 1H), 5.03 (t, $J=4.8$ Hz, 1H), 4.00–3.79 (m, 7H), 2.89 ppm (d, $J=4.8$ Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) $\delta=148.96$, 147.02, 130.61, 125.03, 116.88, 114.84, 107.49, 67.63, 58.54, 43.05 ppm.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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