The Synthesis of Chiral γ-Lactones by Merging Decatungstate Photocatalysis with Biocatalysis

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The implementation of light-driven catalytic processes in biocatalysis opens a golden window of opportunities. We hereby report the merging of photocatalytic C–C bond formation with enzymatic asymmetric reduction for the direct conversion of simple aldehydes and acrylates or unsaturated carboxylic acids into chiral γ-lactones. Tetrabutylammonium decatungstate (TBADT) is employed as the photocatalyst to trigger the hydroacylation of the starting olefins, yielding the corresponding keto esters/acids. Subsequently, an alcohol dehydrogenase converts the intermediate to the chiral alcohol, which undergoes lactonization to the desired γ-lactone. The photochemoenzymatic synthesis of aliphatic and aromatic γ-lactones was thereby achieved with up to >99% ee and >99% yield. This synthesis highlights the power of building molecular complexity by merging photocatalysis with biocatalysis to access high-value added chiral compounds from simple, cheap and largely available starting materials.

Introduction

Building molecular complexity from cheap commodity chemicals is a desirable feature in every synthetic endeavor.[1] An intriguing opportunity is offered by the combination of successive catalytic transformations, wherein each step occurs with a precise control over the regio-chemo- and stereochemical outcome. This is particularly true whenever these transformations are executed in a streamlined fashion, avoiding lengthy separation processes and purification procedures of the involved intermediates. This can limit waste formation and energy consumption, thus boosting the sustainability of the overall process in view of a transition from academia to an industrial setting.[2]

Recently, the combination of enzymes with chemocatalysts (e.g., metal-, organo-, and photocatalysts) has been subject of interest as a very attractive approach for implementing multi-step synthetic processes.[3–4] In this context, the outstanding features of enzymes,[7] such as their broad reaction scope and exquisite selectivity and stereospecificity, make them particularly interesting tools for the preparation of complex and expensive, high-value added (chiral) molecules.[8–10] γ-Lactones are important biologically active molecules and provide building blocks for various fine chemicals (Scheme 1a).[11–16] Moreover, they are highly relevant structures both in the food and cosmetic industries as flavors and fragrances.[24] For instance, γ-decalactone provides a characteristic aroma of peaches.[19,24]

Interestingly, the adoption of a biocatalytic route with the possibility to control the stereochemistry of the final product is particularly suited for constructing this coveted scaffold.[19–21,23,25–30] For this purpose, alcohol dehydrogenases (ADHs) are the elective tools, since these enzymes are capable of reversibly catalyzing the selective reduction of aldehydes and ketones, respectively, to primary and secondary alcohols[31] with high activity and enantioselectivity.[32] In fact, 1,4-keto esters and acids can be conveniently used as starting materials, and upon enzymatic reduction of the carbonyl to the secondary alcohol and acid-promoted lactonization, the desired chiral γ-lactones are obtained with high levels of enantioselectivity (Scheme 1b).[20,21,23,27]

Developing a versatile and robust methodology to form said 1,4-keto esters and acids would allow to harness ADHs’ potential at its fullest extent, thus offering access to a virtually
We initiated our investigations by examining a panel of aliphatic and aromatic aldehydes 1a-f and several electron-poor olefins 2a–c (full list of respective substrates, intermediates and products can be found in the Supporting Information) in the presence of 2 mol% TBADT (Figure 1 and Scheme 2). The photocatalytic reactions were carried out in a home-made photoreactor equipped with 365 nm light-emitting diodes (LEDs, 24 W, Figures S1–2). When employing heptaldehyde 1a (50 mM) and methyl acrylate (1.2 equiv.) dissolved in acetonitrile (MeCN) in a reaction that was irradiated for 24 hours, the desired ketone 3a was obtained in decent yield (13.8 mM; Figure 1).

Interestingly, almost no remaining aldehyde 1a could be detected anymore (< 1 mM). In addition, only trace amounts of heptanoic acid were detected after 24 h reaction. In contrast, when a mixture of acetone/water (Ac/H2O 4:1 v/v) was used as solvent, around 4–5 mM 1a remained after 24 hours of reaction. We thus continued to screen different reaction conditions that would allow for high activity of TBADT, while not impairing the activity of the enzyme in the subsequent step. MeCN, which has been reported to provide both good solubility and good reactivity of the photocatalyst, typically led to higher product formation in most cases; however, in case of 3c, an improved performance could be achieved in Ac/H2O (Figure 1). Next, we screened several ADHs (RasADH from Ralstonia sp.

Results and Discussion

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Figure 1. Photocatalytic synthesis of substituted keto esters 3a–c with olefins 2a–c. Reaction conditions: [aldehyde, 1a] = 50 mM and [acylates, 2a–c] = 60 mM, 2 mol % TBADT, in 1 mL of MeCN or Ac/H$_2$O 4:1 v/v, irradiated with 365 nm UV LED strips for 24 hours. Concentrations have been determined via GC-FID with a calibration based on authentic standards.

Thus, the reactions starting from 1a–f and 2a–c were performed in both, MeCN or Ac/H$_2$O, in order to investigate the effect of the solvent on the efficiency and enantioselectivity of the ADH-catalyzed reaction (Schemes 2 and S1–6). For instance, substrate 3a that resulted from the photocatalytic reaction between 1a and 2a was almost fully reduced by SmCR$_{nat}$ to (R)-4a (95 % yield, 96 % ee) when Ac/H$_2$O was used, and after acidic work-up, readily cyclized to yield (R)-5a with an ee of 96 % and 95 % yield (Scheme 2).

Similarly, the same reaction was performed with all selected ADHs and acrylates 2b–2c and in the presence of MeCN or Ac/H$_2$O (Scheme S1). The desired lactone 5a was obtained with varying yields, while the reduction of the butyl ester 3b was typically less efficient compared to the methyl ester 3a and phenyl ester 3c. Overall, the reduction of 3a by SmCR$_{nat}$ in Ac/H$_2$O and SYADH in MeCN was showing similar results in view of yield, while the reduction of 3c by SYADH gave (S)-5a with the highest ee of > 99 %. Surprisingly, the reductions were typically more efficient when MeCN was used as solvent.

We continued our investigations by performing time course experiments to monitor how fast the enzymatic conversion proceeds (Figure S7a–c). The reactions typically run to completion within 6 hours, while the majority of product is already formed in the first hour. In the time-course experiments, the ee did not significantly change over time, but slightly decreased when increasing amounts of MeCN were used (Table S6).

Building on the results obtained, we became particularly interested in SmCR$_{nat}$ which has been engineered toward the asymmetric reduction of various aliphatic and aromatic γ-keto esters/acids with an excellent ee of > 99 %. Therefore, we expanded our substrate panel to further aliphatic 1b–d and aromatic aldehydes 1e–f (Scheme 2). Similar to the photochemoenzymatic reactions performed with aldehyde 1a and acrylates 2a–c, aliphatic lactones (R)-5b and (R)-5c were obtained with high yields (up to 99 %) and ee’s (up to 98 %) with SmCR$_{nat}$ while reactions with SYADH gave the corresponding lactones (S)-5b and (S)-5c with good ee (up to 93 %). We continued to investigate the conversion of aromatic aldehydes 1e–f and acrylates 2a–c with our ADH panel. RasADH showed high yield for the aromatic lactone (S)-5e in MeCN (> 99 % yield), while in Ac/H$_2$O the yield was lower (84 %), although a higher ee (99 %) was observed. Similarly, all possible substrate combinations have been explored with our ADH panel (Schemes S1–6). Overall, depending on the chosen ADH and reaction conditions (MeCN or Ac/H$_2$O), the lactone yields and enantioselectivities obtained with RasADH and LKADH typically lacked behind the performance of SmCR$_{nat}$ and SYADH. Nonetheless, both enantiomers of the respective lactones 5a–d and 5f were obtained with either SmCR$_{nat}$, LKADH or SYADH with high yields of up to 99 % (e.g., for (S)-5a) and good to excellent enantioselectivities (Scheme 2). The only exception is 5e, for which only the (S)-enantiomer could be obtained with our chosen ADH panel. Overall, the photochemoenzymatic approach enabled the direct conversion of simple aldehydes 1a–f and olefins 2a–c into the respective keto esters 3a–r, which are further converted to yield the desired γ-lactones 5a–f after acid-promoted lactonization.
While the conversions and enantioselectivities achieved with acrylates 2a–c were encouraging, we became interested in replacing the acrylates with fumaric acid 2d, offering the advantage of being less volatile and prone to undergo side reactions (e.g., oligomerization). Moreover, fumaric acid was recently shown to be an excellent substrate for the preparation of γ-keto acids under TBADT-photocatalyzed conditions in the presence of aldehydes, outperforming the performance offered by olefins substituted with a single electron-withdrawing group. Thus, the process initially led to a dicarboxylic acid adduct, which spontaneously underwent decarboxylation to afford the desired product (Figure 2).

Accordingly, we first investigated whether the C–C bond formation between our aldehydes panel 1a–f and 2d under conditions compatible with the follow-up biocatalytic step can be efficiently catalyzed by TBADT (Figure 2). Similar to the reactions with the acrylates, we studied the photocatalytic synthesis in the presence of MeCN/H$_2$O (water was here required to ensure full solubility of the reaction components) or Ac/H$_2$O, starting from a higher (100 mM) substrate concentration. Furthermore, while reactions with acrylates 2a–c have been irradiated at 365 nm, it was more convenient to adopt 395 nm light irradiation to promote the desired acylation of 2d (Table S7). Thus, the highest conversion was achieved for 1d with 2d, yielding 92 mM of 3v. While in reactions with 2a–c the acrylates had to be applied in excess due to the high volatility of these compounds, equimolar amounts of aldehydes 1a–f and 2d could be used and much better mass balances were consistently observed. Interestingly, the reaction time had to be significantly prolonged to 40 hours, because in case of 1d–f remaining aldehyde (≤5–7 mM) was still detected.

Scheme 2. The photochemoenzymatic synthesis of chiral γ-lactones starting from simple aldehydes and acrylates. The first step comprises the photocatalytic C–C bond formation catalyzed by TBADT under UV light irradiation (365 nm) to the corresponding keto esters, followed by an ADH-promoted asymmetric reduction to the corresponding hydroxy esters, which fully lactonize under acidic conditions to the desired γ-lactones. Photocatalytic reaction conditions: [aldehyde, 1a–f] = 50 mM and [acrylates, 2a–c] = 60 mM, 2 mol% TBADT, in 1 mL of either MeCN or Ac/H$_2$O (4:1 v/v), irradiated with 365 nm LEDs for 24–30 hours. Enzymatic reaction conditions: 3a–r = [6.25% (v/v) from photocatalytic step], Glucose (50 mM), NADP$^+$ (0.5 mM), purified E. coli/BmGDH (0.2–0.5 kU/mL), cell free extract of ADHs (100 mg/mL), in 0.5 mL buffer solution 50 mM KPi, pH 7.5 or 100 mM NaPi pH 7 (in the case of SmCRm4), 30 °C, 24 h. Analytical yields determined by GC-FID are reported.
Next, we combined the photocatalytic keto acid synthesis with the enzymatic reduction catalyzed by our ADH panel (Scheme 3). SmCR<sub>red</sub> showed comparable activity toward the medium-chain keto acids as for the respective keto esters (Figure S4). In particular, the selectivity for these substrates was high, and the corresponding (R)-lactones 5a-c could be obtained with an ee of up to >99% (Scheme 3 and S7). Similarly, the (R)-lactones 5a-c were obtained with RasADH, while yields were in general higher compared to reactions performed with SmCR<sub>red</sub> and the enantioselectivity was slightly lowered. In another example, RasADH produced up to 5.8 mM of the aromatic lactone (R)-5d with excellent yield (>99%) and 94% ee (Scheme 3).

The corresponding (S)-lactones 5a-c were obtained with SYADH; however, enantioselectivity was typically only moderate, except for (S)-5a that was obtained with >99% yield and 97% ee, providing 4 mM of final product. As observed for the reactions with keto esters (Scheme 2), the solvent had a strong effect on the efficiency of the ADH-catalyzed reduction. The γ-lactones 5d-f were predominantly obtained by RasADH and SYADH (Scheme 3 and S7), and reactions performed in MeCN/H<sub>2</sub>O typically gave higher yields. In particular, (R)-5d, (S)-5e and (R)-5f were obtained with good selectivities of up to 96% ee.

To further demonstrate the synthetic usefulness of this photochemoenzymatic approach, we performed semi-preparative scale synthesis of a few selected γ-lactones ((S)-5a, (R)-5b, (R)-5c, (R)-5d, (S)-5e, (S)-5f) at a volume of 12 mL. For the majority of products, good to excellent enantiocontrol (up to 99% ee) and analytical yields were obtained (72 to >99%). For instance, RasADH showed high catalytic activity in the synthesis...
of (R)-5c. After 24 hours, 98% 3u was converted to afford (R)-5c in 85% yield of the isolated product (11 mg product) and with 96% ee. Similarly, (S)-5e was obtained with 53% isolated yield (4 mg) and 99% ee (Table S8 and Figures S14–19). While the conversions showed high catalytic activity of the respective ADHs, the obtained isolated yields were only between 39–85%. This can mainly be attributed to the loss of lactones during product isolation due to high volatility, although a combination of chromatography and liquid-liquid extraction methods was investigated.

Conclusion

In conclusion, a convenient methodology to enantioselectively produce γ-lactones from simple starting materials via photocatalytic C–C bond formation and enzymatic asymmetric reduction has been realized. While it facilitates the enantioselective synthesis of various aliphatic γ-lactones as highly important flavor and fragrance compounds, the product scope even comprises several aromatic γ-lactones, which are frequently used precursors for the preparation of pharmaceuticals. While this is the first report to combine decatungstate-catalyzed lactonization reaction due to high volatility, although a combination of chromatography and liquid-liquid extraction methods was investigated.

Experimental Section

Gene cloning and expression of alcohol dehydrogenases

General information on strains and plasmids, and the details of gene cloning protocols can be found in the Supporting Information, “Sections Bacterial Strains, Plasmids and Primers”. Site-directed mutagenesis was performed according to the Stratagene Quick-Change™ protocol, using primers as listed in the Supporting Information. The presence of the desired mutations in all constructs was verified by sequencing. Escherichia coli BL21(DE3) was used as expression strain for all ADHs. Plasmids containing the adh genes were isolated and transformed into E. coli BL21(DE3) by the heat shock method. Cells were routinely cultivated from a single fresh colony. E. coli BL21(DE3) cells carrying the RasADH, SYADH, LKADH, and SmCRαα plasmids, respectively, were grown in 400 mL TB medium with the respective antibiotic (40 μg/mL kanamycin or 100 μg/mL ampicillin in case of LKADH). For RasADH, the medium was further supplemented with 0.6 mM CaCl₂. The medium was inoculated with an overnight culture to give an OD₆₀₀ of 0.05. Cells were grown in 2 L baffled shake flasks at 37°C until an OD₆₀₀ of 0.6–0.8 was reached and induced by the addition of isopropyl-β-D-thiogalactopyranoside (IPTG) to a final concentration of 1 mM for LKADH, 0.5 mM for SYADH and RasADH and 0.2 mM for SmCRαα. For SmCRαα induced cultures were incubated for 24 hours at 16°C before harvesting the cells by centrifugation (3,400 x g for 15 min) at 4°C and washing with sodium phosphate buffer (100 mM, pH 7). For all others, induced cultures were incubated for 20 hours at 20°C before harvesting the cells by centrifugation (1,344 x g for 15 min) at 4°C and washing with potassium phosphate buffer (50 mM, pH 7.5). Cell pellets were centrifuged again with the same speed and resuspended in the same washing buffer to give a wet cell weight (W CW) of 300 g dry/L. Cell disruption was performed using ultrasonication with 70% duty cycle, out-put 7–8 sec for 2 min. Cell debris was separated from the crude extract by centrifugation (16,000 x g, 45 min, 4°C). The crude cell extracts were filtered (0.45 μm, Whamast®) and aliquoted to be stored at –20°C.

Photochemoenzymatic synthesis of chiral γ-lactones

The photocatalytic reactions were performed in 2 mL glass vials. A mixture of aldehydes (50 mM, 1 equiv.), acrylates (60 mM, 1.2 equiv.), and a catalytic amount of TBADT (2 mol%, 1 mM) was dissolved in 1 mL acetonitrile or acetonitrile/water (4:1 v/v). In case of fumaric acid reactions, a mixture of aldehydes (0.1 M, 1 equiv.) and fumaric acid (0.1 M, 1 equiv.) in the presence of a catalytic amount of TBADT (2 mol%, 2 mM) was dissolved in 1 mL either MeCN/H₂O (9:1 v/v) or Ac/H₂O (4:1 v/v). The resulting solutions were purged with nitrogen for 3 minutes, screw-capped and irradiated at 365 nm or 395 nm by using a home-made light-setup (24 W; see Supporting Information, “Section Photocatalytic Setup” and Figures S1,2 for further details). The light reactor was then placed into a shaking incubator and reactions were incubated at 24°C and 220 rpm for 24–40 h. After the reaction was complete (aldehyde consumption was monitored via GC-FID), 6.25% of reaction solution containing the corresponding γ-keto esters or γ-keto acids was transferred to a new 2 mL glass vial. To this solution, the crude cell extract containing the overexpressed (R)- or (S)-selective ADHs (70–200 mg/mL), glucose (50 mM), NADP⁺ (0.5 mM), and purified BmGDH (0.2–0.5 KU/mL) were added. To reach the total reaction volume of 0.5 mL, 50 mM KPi buffer at pH 7.5 or 100 mM NaPi buffer at pH 7 in case of SmCRαα was added. The mixture was then stirred in a thermomixer at 30°C, 700 rpm under dark conditions. After 20–24 h, the reaction was terminated by adding 0.1 M sulfuric acid (95–97%), and the reaction samples (200 μL) were extracted with ethyl acetate (200 μL) and dried with a spatula tip of MgSO₄, after incubating at RT for 1 h. Analytical yields and enantioselectivity of lactones were directly determined by GC-FID. Details of columns and analytical methods, with chromatograms, can be found in the Supporting Information, “Section GC analytics”.

Semi-preparative scale syntheses

In a 2 mL glass vial, a mixture of aldehyde (0.1 M, 0.1 mmol, 1 equiv.) and fumaric acid (0.1 M, 0.1 mmol, 1 equiv.) in the presence of a catalytic amount of TBADT (2 mol%, 2 mM) were dissolved in 1 mL MeCN/water (9:1 v/v). In case of acrylate reaction, aldehydes (0.1 M, 0.1 mmol, 1 equiv.), acrylates (0.12 M, 0.12 mmol, 1.2 equiv.) and a catalytic amount of TBADT (2 mol%, 2 mM) was dissolved in 1 mL Ac/water (4:1 v/v). The resulting solutions were purged with nitrogen for 3 minutes, screw-capped and irradiated at either 365 nm or 395 nm by using the home-made light-setup. The light reactor was placed into a shaking incubator and reactions were incubated at 24°C and 220 rpm for 30–40 h. 6.25% of the reaction solution containing the corresponding γ-keto esters/acid was transferred to a new 20 mL glass vial. To this solution, the crude cell extract containing the overexpressed (R)- or (S)-selective ADHs (100 mg/mL), glucose (50 mM), NADP⁺ (0.5 mM), and purified BmGDH (0.2–0.5 KU/mL) were added. To reach the total reaction volume of 12 mL, 50 mM KPi buffer at pH 7.5 or 100 mM NaPi buffer at pH 7 in case of SmCRαα was added. The reactions were placed in an incubation shaker at 30°C, and were incubated at 180 rpm for 20–24 h under dark conditions. The reaction mixture was then extracted with DCM (3 times) after acidification at pH 2.0 using 0.5 M aqueous H₂SO₄. The lactonization reaction was carried out at RT and 180 rpm for 1 h. The organic layer was dried over anhydrous MgSO₄ followed by the addition of trifluoroacetic acid.
The reaction mixture was maintained with saturated aqueous NaHCO₃ (10 mL) and subsequently extracted with DCM (3 × 10 mL). The organic phase was separated and dried over MgSO₄, and then concentrated in vacuum. The lactones were purified via column chromatography eluting with a mixture of ethyl acetate and pentane (1:4) to provide the pure γ-lactones. ¹H NMR (500 MHz) spectra were recorded in CDCl₃. Isolated yields were determined by calculating the amount of purified product obtained.

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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 from the corresponding author upon reasonable request.

Keywords: photobiocatalysis · C–C bond formation · decatungstate anion · asymmetric reduction · alcohol dehydrogenases

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