EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801819

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801819

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FULL PAPER

Synthesis of enantiomerically pure 5,6-dihydropyran-2-ones via chemoenzymatic sequential DKR-RCM reaction

Dominik Koszelewski, Filip Borys, Anna Brodzka, Ryszard Ostaszewski*

We would like to dedicate this paper to Professor Nicholas Turner on occasion of his 58th birthday

Abstract: The enantiomerically pure 5,6-dihydropyran-2-ones play a crucial role as the building blocks in the synthesis of various bioactive compounds. A new straightforward protocol toward enantiomerically pure 5,6-dihydropyran-2-ones based on enzymatic dynamic kinetic resolution (DKR) resulted in non-racemic homoallylic crotonates sequentially combined with ring-closing metathesis (RCM) was designed. The influence of the reaction conditions on the catalytic behavior of selected hydrolases in the synthesis of non-racemic homoallylic crotonates was investigated. Under optimized conditions for enzymatic DKR desired homoallylic esters were obtained with high yields and enantiomeric excesses exceeding 99%. Finally, established enzymatic DKR was successfully combined as a two-steps sequential procedure with RCM affording target 5,6-dihydropyran-2-ones with high yields up to 75% and enantiomeric excesses exceeding 99%.

Introduction

The lactone rings are vital structural feature in organic chemistry because it is present in many natural products isolated form vast range of living organisms (Figure 1).[1] Particularly, the unsaturated 5,6-dihydropyran-2-ones exhibits variety of potent biological activities. This class of lactones have been found to act as protein phosphatase inhibitors[2], be cytotoxic,[3] display an anti-inflammatory,[4] antibacterial,[5] and anticancer activity.[6] Some of these pharmacological properties can be explicated by the conjugated double bond present in its structure, which can behave as a Michael acceptor in the presence of proteins in biological systems.[7] The beneficial or adverse effects of these compounds depend on their absolute configuration making separation of two enantiomers from racemic mixture an important issue, particularly in the pharmaceutical industry, because of the different pharmacological activities and pharmacokinetic characteristics of each enantiomer.[8] Additionally, the lactone motif exists in many flavors components and hence is employed in the perfume and food industry.[9] Moreover, presence of double bond in structure of these compounds allow its transformation into chiral more complexed molecules possessing high importance in medicinal industry.[10] As a consequence, there has been an increasing interest in synthetic studies of *δ*-lactones.[11]

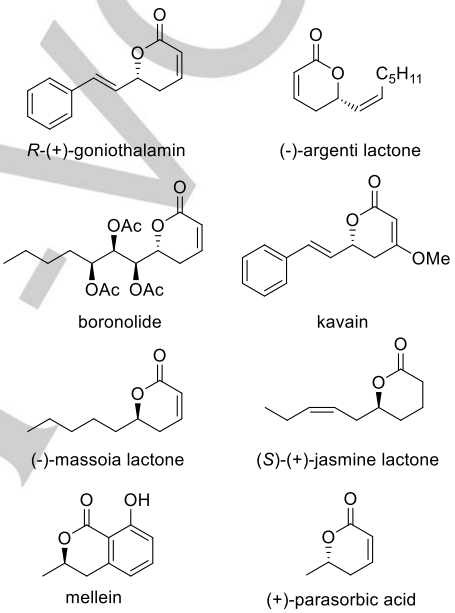

Figure 1. Selected examples of naturally occur α,β-unsaturated δ-lactones.

The development of economic and environmentally sustainable methodologies for the synthesis of target none-racemic lactones remains a challenge, because conventional processes often lead to significant amounts of wastes and/or are performed under harsh reaction conditions. Intriguingly, most of these methods suffer from poor enantioselectivity and often require environmentally hazardous, expensive metal catalysts and products require complex purification procedures.[12] Due to pharmacopoeia limits of heavy metal contaminations (below 5 ppm) reported methods cannot be used in the pharmaceutical and cosmetic industry. Therefore, development of a catalyst system that do not contain harmful components like transition metals, strong acids or bases seems desirable. Enzymes are highly efficient biocatalysts researched for industrial-scale synthesis because of their several distinct advantages that range from their operation under milder reaction conditions, to their exceptional enantioselectivity, and to their lower environmental and physiological impact.[13] As such, their lower energy requirements, mitigation of waste generation, and simplified production routes have been partially realized in the pharmaceutical, food, and beverage industries.[14] Although some chemical procedures have been developed to provide the routes to target lactones,[15] only a

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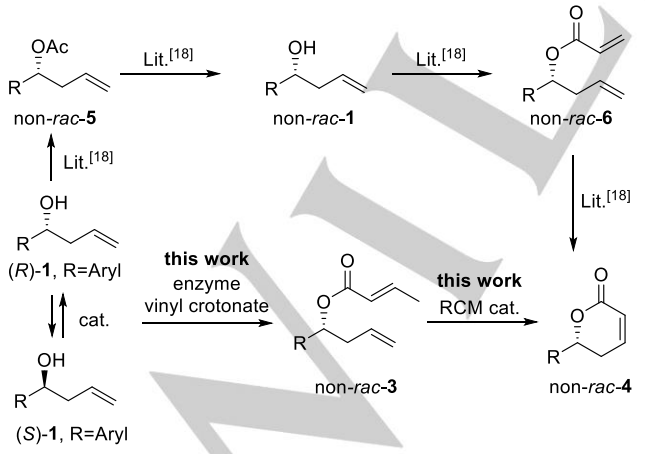
Supporting information available: Experimental procedures, ^{1}H NMR, ^{13}C NMR spectra.

few are based on enzymatic approaches. Those protocols comprise of promiscuous aldol reaction,[16] enzymatic oxidation,[17] or lipase-catalyzed kinetic resolution of 1,5-diols.[18] There are some reports in literature on combination of enzyme catalyzed transesterification of secondary alcohols with unsaturated vinyl ester as the acyl donors,[19,20] as well as hydrolytic kinetic resolution (KR) of acrylates with ring-closing metathesis (RCM) reaction.[21] The major disadvantage of such methodology is maximum 50% yield of desired product in its enantiomerically pure form.[22] This drawback can be overcome by combination of *in situ* racemization of substrate enantiomers with enzymatic resolution resulting in dynamic kinetic resolution (DKR).[23]

Homoallylic alcohols are common substrates for the synthesis of enantiomerically enriched lactones.[24] Several studies have been reported on dynamic kinetic resolution of homoallylic alcohols. Surveys such as that conducted by Kanerva and Leino in 2011 showed the DKR of *rac*-1-phenyl-3-buten-1-ol, but prolonged reaction time (up to 168 h) was required.[25] Recently, Bäckvall *et al*. proposed lipase catalyzed DKR of homoallylic alcohols with ruthenium racemization catalyst. Although proposed strategy provided acetates **5** with high enantiomeric excess and high yields still required several additional chemical steps for transformation of product into acrylates **6** which after RCM provided desired 5,6-dihydropyran-2-ones (Scheme 1).[26] In continuation to our previous work on enzyme catalyzed route to optically active *δ*-lactones based on enzymatic kinetic resolution of racemic (*E*)-methyl 5-(aryl)-5-hydroxypent-2-enoates,[27] herein we are reporting a new straightforward protocol for the synthesis of enantiomerically pure lactones **4**. The former methods rely on the enzymatic acylation of racemic precursors using vinyl, isopropenyl or 4-chlorophenyl acetates as an acyl group donors, an obvious drawback of them is necessity to perform an additional not trivial step to recover hydroxy group towards further functionalization. Thus, it seems significant to find a method to overcome these limitations.

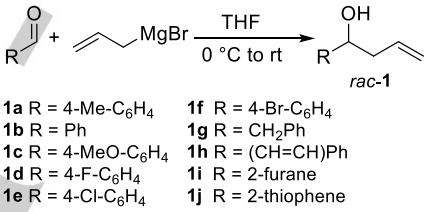


Scheme 1. Synthetic strategies toward enantiomerically enriched 5,6-dihydropyran-2-ones (**4**).

As an alternative to existing synthetic methods toward enatiomerically enriched 5,6-dihydropyran-2-ones (**4**) which is mainly based on multi-step transformations of racemic homoallylic alcohols (**1**), we propose sequential protocol which intend to combine enzymatic DKR of various racemic homoallylic alcohols (**1**) with vinyl crotonate as the acyl donor and subsequent RCM reaction affording target enatiomerically pure 5,6-dihydropyran-2-ones (**4**) in only two steps (Scheme 1).

Results and Discussion

Synthesis of homoallylic alcohol substrates: The model substrates racemic homoallylic alcohols (**1a**-**j**) were synthesized according to the literature procedure in Grignard reaction starting from the corresponding aldehydes and allylmagnesium bromide (see the Supporting Information).[26] This procedure afforded racemic homoallylic alcohols **1a-j** with yields up to 68% (Scheme 2).



Scheme 2. Synthesis of racemic homoallylic alcohols **1a**-**j**.

Enzymatic dynamic kinetic resolution of homoallylic alcohols: In order to establish efficient DKR process first the enzymatic kinetic resolution of 1-(4-methylphenyl)-3-buten-1-ol (*rac*-**1a**) as a model substrate was conducted screening several commercially available lipases (see the Supporting Information). The reaction was performed in dry toluene at 60 °C with the vinyl crotonate (1.5 equiv.) as an acyl group donor. Among tested biocatalysts, immobilized lipase form *Mucor miehei* (Lipozyme), polymer supported *Candida antarctica* lipase B (Novozyme 435), and native *Candida cylindracea* lipase showed activity under studied conditions providing desired crotonate **3a** (see the Supporting Information). Obtained results remain in agreement with literature data regarding preserved activity of these enzymes in their native and immobilized state at elevated temperatures.[28] Unfortunately, Lipozyme and *Candida cylindracea* lipases exhibited low enantioselectivity[29] (*E*=6), only Novozyme 435 stood out sufficient enantioselectivity (*E*=120) providing *R*-enantiomer of crotonate **3a** with 98% enantiomeric excess (Table S1, supporting information). The application of native lipase B from *Candida antarctica* under analogous conditions at 60 °C resulted in desired product (*R*)-**3a** with low performance. It was recognized that, beside high temperature, acetaldehyde arises from the used vinyl esters can adversely affect both enzyme activity and enatioselectivity.[30] These inconveniences may be overbear by the application of the proper immobilization technique.[31] Moreover, additional studies with various organic

solvents revealed that initially selected toluene was the most suitable medium[32] for examined reaction with Novozyme 435 (Table S2, supporting information). Since a highly enantioselective enzyme-catalyzed acylation[33] is required for obtaining enantiomerically enriched crotonates **3** by DKR, Novozyme 435 was selected for further studies. This enzyme has also been shown to possess a very high thermostability, tolerating temperatures as high as 100 °C,[28f] which makes this robust catalyst even more suitable for undertaken studies.

Having in hands results from enzymatic kinetic resolution we turned our attention to develop DKR protocol. The classical and commonly applied domino metal−enzyme DKR is based on *sec*-alcohol racemization and enzymatic acylation of the preferred enantiomer.[34] In the case of chiral alcohols the racemization predominantly occurs through a hydrogen transfer process.[35] According to recent reports, a second generation ruthenium catalyst **2**, $[Ru(CO)_2Cl(\eta^5\text{-}C_5Ph_5)]$ (Figure 2) has been applied with enzymes in DKR protocol for the racemization of homoallylic alcohols and scaled-up to > 100 g scale.[26,36]

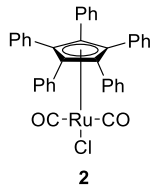


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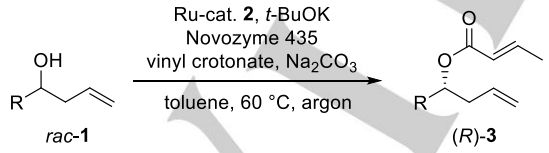
Figure 2. Structure of catalyst **2** used for DKR reaction.

Initially, the racemization of (*S*)-**1a** was studied in dry toluene at 20 °C and 60 °C under inert atmosphere. At low temperature racemization rate was insufficient and after 6 hours *ee* of (*S*)-**1a** still was 60%. The slow racemization may be explained by coordination of the double bond of used substrates to ruthenium in the alkoxide intermediate thus blocking the coordination site required for β-hydride elimination.[37] Increase of temperature to 60 °C led to the substantial surge of racemization rate and enantiomeric excess dropped from 100 to 7% within 10 minutes (Figure S1, supporting information).



Scheme 3. Dynamic kinetic resolution of homoallylic alcohols *rac*-**1**.

Promising data collected from separate investigation on the racemization and enzyme kinetic resolution encouraged us to combine these two processes in DKR protocol. DKR of selected racemic substrates **1a**, **1b** and **1j** was performed on a 1 mmol scale utilizing 5 mol% of catalyst **2** at 60 °C (Scheme 3). The results are summarized in Table 1.

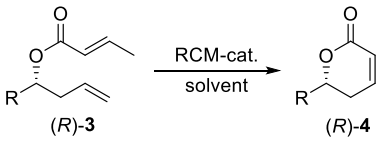
Table 1. Dynamic kinetic resolution of homoallylic alcohols *rac*-**1**.[a]

Entry	Substrate	*t* [d]	Yield [%][b]	*ee* (*R*)-**3** [%][c]
1	**1a**	5	99 (69)	>99
2	**1b**	5	99 (73)	91
3	**1j**	5	99 (78)	96

[a] Reaction conditions: $[Ru(CO)_2Cl(\eta^5\text{-}C_5Ph_5)]$ **2** (0.05 mmol), *t*-BuOK (0.5 M solution in THF, 0.05 mmol), substrate *rac*-**1** (1 mmol), Novozyme 435 (10-100 mg·mmol^{-1}), Na_2CO_3 (1 mmol), vinyl crotonate (1.5 mmol), toluene (2 mL) at 60 °C under argon. [b] Determined by ^{1}H NMR spectroscopy. Yield of isolated product **3** after chromatography in parentheses. [c] Determined by chiral HPLC.

The crotonates (*R*)-**3** were isolated by column chromatography. Enzymatic resolution with racemization of substrate catalyzed by ruthenium catalyst of *rac*-**1a** provided desired enantiopure 4-(*p*-methylphenyl)-1-butene crotonate ((*R*)-**3a**) in high yield (Table 1, entry 1). Obtained result indicated that Novozyme 435 is enantiospecific biocatalyst.[38] However, a slightly lower enantioselectivity was observed for alcohols *rac*-**1b** and *rac*-**1j** (Table 1, entries 2 and 3), but still *ee* values remained high (91% and 96%, respectively). Obtained data correspond to the previously reported one for the DKR of the same allylic alcohols with isopropenyl acetate as an acyl donor.[25,26]

The Ring-Closing Metathesis (RCM) for crotonic esters 3: The next step of our studies was to optimize conditions for ring-closing metathesis reaction. RCM was performed on 1 mmol scale (Scheme 4).



(*R*)-**3** (*R*)-**4**

Scheme 4. RCM of crotonic esters **3**.

The influence of temperature, solvent and Grubbs' catalyst amount on the reaction yield were studied. RCM of (*R*)-**3a** proceeded well with a 10 mol% Grubbs 2nd generation catalyst in dry toluene at 80 °C. The 5,6-dihydropyran-2-one (*R*)-**4a** was isolated in 78% yield after 2 hours of reaction. Moreover, enantiomeric excess of isolated solid product (*R*)-**4a** was higher than enantiomeric excess of substrate (*R*)-**3a** (Table 2, entry 1). Obtained result clearly shown that upon RCM reaction racemization of the target (*R*)-**4a** does not occur.

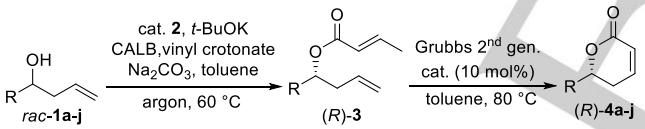
Table 2. Optimization of RCM reaction conditions.[a]

Entry	**3**	Solvent	Grubbs' catalyst	Amount of catalyst	Yield **4** [%]

1	**3a**	toluene	II	10 mol%	78[b] (99% *ee*)
2	**3a**	toluene	II	10 mol%	70[c]
3	**3a**	toluene	II	5 mol%	65
4	**3a**	toluene	II	15 mol%	79
5	**3a**	toluene	I	10 mol%	56
6	**3a**	DCM	II	10 mol%	59[d]
7	**3a**	DCE	II	10 mol%	53
8	**3a**	cyclohexane	II	10 mol%	72
9	**1i**	toluene	II	10 mol%	84

[a] Reaction conditions: substrate (10^{-3} M), Grubbs' catalyst 1st or 2nd gen. in dry toluene stirred at 80 °C for 2 h. [b] Substrate (*R*)-**3a** *ee* =97%. [c] Reaction time 12 h [d] Reaction at 40 °C

Extending of reaction time to twelve hours did not improved reaction yield (Table 2, entry 2). Application of 5 mol% Grubbs 2nd generation catalyst caused drop in reaction yield to 65%. The increase of catalyst loading to a 15 mol% did not affected the reaction yield. When dichloromethane (DCM) was used as the reaction medium and temperature was lowered to 40 °C product *rac*-**4a** was isolated in 59% yield (Table 2, entry 6). The use of dichloroethane (DCE) or cyclohexane as a solvent did not result in increased yield of *rac*-**4a** (Table 2, entry 7-8). Under optimized reaction conditions another ester *rac*-**4i** was transformed to the corresponding unsaturated lactone with high 84% yield.



Scheme 5. Sequential, two step chemoenzymatic DKR-RCM protocol.

Table 3. Sequential, two step chemoenzymatic DKR-RCM protocol.[a]

Entry	Substrate	Yield **4**[b]	*ee* (*R*)-**4**[c]
1	**1a**	55	99
2	**1b**	58	97
3	**1c**	70	94
4	**1d**	70	97
5	**1e**	57	95
6	**1f**	58	99
7	**1g**	63	>99[e]
8[d]	**1h**	58	96
9	**1i**	70	>99[e]
10	**1j**	75	>99[e]

[a] Reaction conditions: DKR: $[Ru(CO)_2Cl(\eta^5\text{-}C_5Ph_5)]$ **2** (0.05 mmol), *t*-BuOK (0.5 M solution in THF, 0.05 mmol), substrate *rac*-**1** (1 mmol), Novozyme 435 (10-100 mg·mmol^{-1}), Na_2CO_3 (1 mmol), vinyl crotonate (1.5 mmol), toluene (2 mL) at 60 °C under argon. RCM: substrate (10^{-3} M), Grubbs' catalyst 2nd gen. in dry toluene stirred at 80 °C for 2 h [b] Yield of isolated product **4**. [c] Determined by chiral HPLC or by comparison of optical rotation with literature data. [d] The reaction was run at room temperature. [e] Established by the comparison of optical rotations power with literature data (supporting materials).

Combination of DKR and RCM in sequential, two-step procedure: With results from separate studies on the DKR and RCM in hand, their successful combination in sequential procedure was feasible. Unfortunately, addition of Grubbs' 2nd generation catalyst to reaction mixture after DKR resulted in complicated mixture of product. The performance of Grubbs' 2nd generation catalyst in presence of acrylic support of Novozyme 435 can be undermined by Michael addition pathways enabled by free PCy_3, which limit yields, promote side-reactions, and cause catalyst decomposition.[39] Hence, reaction mixture after enzymatic dynamic kinetic resolution was filtered through a short pad of silica and washed with 5% ethyl acetate in pentane and evaporated under reduced pressure. In the next step RCM reaction was performed. This protocol provided desired 5,6-dihydropyran-2-ones in good to high yield and with high to excellent enantiomeric excess (Scheme 5). The results are summarized in Table 3. Electron-withdrawing as well as electron-donating substituents in the *para*-position of aromatic ring turned out to be compatible with the catalytic system (Table 3, entries 1-6). Substrates with heterocyclic ring *rac*-**1i** and *rac*-**1j** also showed high compatibility with developed protocol (entries 9 and 10). The DKR reaction with substrate *rac*-**1h** was performed at room temperature due to the site formation of 4-oxo-6-phenyl-1-hexene as a byproduct form starting material isomerization.

Conclusions

In summary, we have developed sequential, two-step chemoenzymatic procedure toward target unsaturated *δ*-lactones based on enzymatic dynamic kinetic resolution using vinyl crotonate, followed by ring-closing metathesis. Since the native biocatalysts displayed moderate activity under studied conditions substantially robust immobilized enzymes were applied. Among them lipase B from *Candida antarctica* immobilized on acrylic support (Novozyme 435) revealed to be enatiospecyfic in respect to selected homoallilic alcohols providing enantiopure crotonates. Further, the desired 5,6-dihydropyran-2-ones were isolated in good to high yields and with enantiomeric excesses exceeding 99%. Elaborated protocol which combine successfully two succeeding catalytic processes, dynamic enzymatic kinetic resolution and metal catalyzed RCM reaction, turned out to be compatible with homoallylic crotonates possessing electron-withdrawing as well as electron-donating substituents on the aromatic ring. Moreover, synthetically challenging heterocyclic

furan and thiophene derivatives were found to be suitable substrates for established procedure. The protocol reported here should be a useful complement to known methods as allows easy and efficient synthesis of biologically relevant 5,6-dihydropyran-2-ones and the corresponding *δ*-lactones in enantiopure form for vast range of homoallylic alcohols.

Experimental Section

Materials and general methods

All the chemicals were obtained from commercial sources and the solvents were of analytical grade. Immobilized lipases from *Mucor miehei* (Lipozyme) and *Candida cylindracea* were purchased from Sigma-Aldrich. Immobilized lipase from *Candida antarctica* (Novozyme 435) was purchased from Novo Nordisk. Column chromatography was performed on Merck silica gel 60/230-400 mesh. Enzymatic reactions were performed in a vortex (Heidolph Promax 1020) equipped with incubator (Heidolph Inkubator 1000). To prove the ability of the established protocol each reaction was repeated at least three times.

General procedure for DKR reaction. To a Schlenck flask, Novozyme 435 (100 mg/mmol), sodium carbonate (1 equiv.) and ruthenium catalyst **2** (5 mol%) were added under argon atmosphere. Next, toluene (1.0 mL) and then *t*-BuOK (100 µL of a 0.5 M solution in THF, 5 mol%) were added and mixture was stirred for 5 minutes at 60 ºC. After that time, *rac*-**1** (1.0 mL of a 1.0 M solution in toluene, 1 equiv.) was added and incubated at 60 ºC for 5 minutes. Next vinyl crotonate (1.5 mmol, 1.5 equiv.) was added and reaction was stirred for 5 days and next filtrated through a silica pad and washed with ethyl acetate. The products were isolated by flash chromatography (hexanes/ethyl acetate).

General procedure for chemoenzymatic DKR-RCM reaction. To a Schlenck flask Novozyme 435 (100 mg/mmol), sodium carbonate (1 equiv.) and ruthenium catalyst **2** (5 mol%) were added under argon atmosphere. Next, toluene (1.0 mL) and then *t*-BuOK (100 µL of a 0.5 M solution in THF, 5 mol%) were added and mixture was stirred for 5 minutes at 60 ºC. After that time *rac*-**1** (1.0 mL of a 1.0 M solution in toluene, 1 equiv.) was added and incubated at 60 ºC for 5 minutes. Next vinyl crotonate (1.5 mmol, 1.5 equiv.) was added and reaction was stirred for 5 days and next carefully filtrated through a silica pad with ethyl acetate and filtrate was evaporated under reduced pressure. The remaining mixture was diluted with dry toluene to final concentration (10^{-3} M). Next, 10 mol % Grubbs 2nd generation catalyst was added and resulting mixture was stirred for 2 hours at 80 °C. After that time solvent was evaporated and the product **4** was isolated by flash chromatography.

Acknowledgements

This work was supported by Polish National Science Center project No. 2016/23/B/ST5/03307.

Keywords: domino reaction • *δ*-lactones • dynamic kinetic resolution • metathesis • homoallylic alcohols

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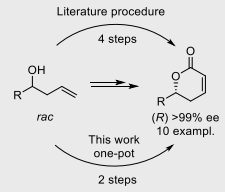

*Dominik Koszelewski, Filip Borys, Anna Brodzka, Ryszard Ostaszewski**

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Synthesis of enantiomerically pure 5,6-dihydropyran-2-ones via chemoenzymatic sequential DKR-RCM reaction

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