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Kirmse-Doyle- and Stevens-type Rearrangements of Glutarate-derived Oxonium Ylides

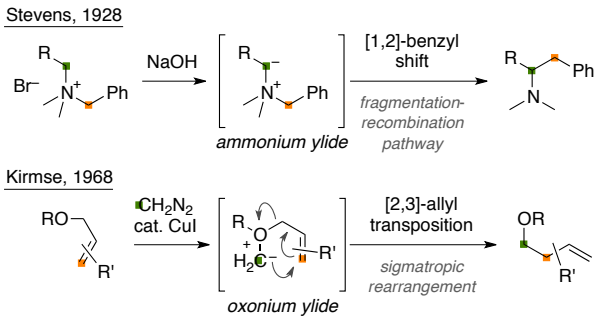
Benedikt Skrobo,[a] Nils E. Schlörer,[a] Jörg-M. Neudörfl,[a] and Jan Deska*[a,b]

Abstract: A novel chemoenzymatic synthetic cascade enables the preparation of densely decorated tetrahydrofuran building blocks. Here, the lipase-catalyzed desymmetrization of 3-alkoxyglutarates renders highly enantioenriched carboxylic acid intermediates, whose subsequent activation and oxonium ylide rearrangement by means of rhodium or copper complexes furnishes functionalized *O*-heterocycles with excellent diastereoselectivity. The two-step protocol offers a streamlined and flexible synthesis of tetrahydrofuranones bearing different benzylic, allylic or allenylic side chains with full control over multiple stereogenic centers.

Introduction

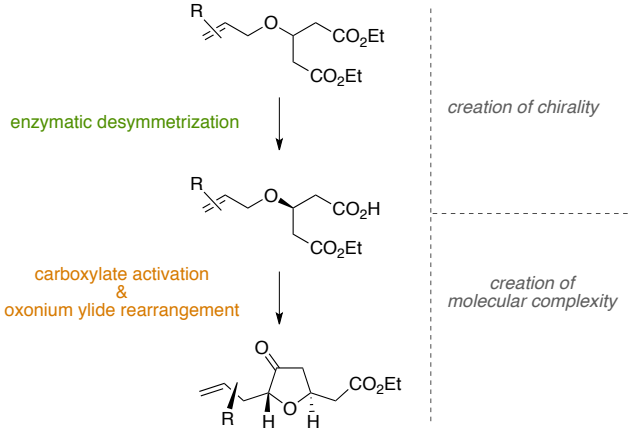
Among the various enzymatic approaches towards optically active building blocks,[1] the conversion of symmetrical homo-bifunctional molecules by lipase-catalyzed selective transformations of ester, alcohol or amine groups represents a particularly powerful tool.[2] Biocatalytic desymmetrizations render synthetically attractive, enantioenriched, and orthogonally prefunctionalized structural entities as valuable starting materials for the preparation of intriguing target architectures.[3] At the same time, the enzymatic manipulation of enantiotopic groups allows for a theoretical yield of 100% as opposed to the more commonly employed kinetic resolution approach. An intrinsic drawback in this design, however, is that the required enzyme substrates most often lack pronounced complexity and that the early-stage character of enantioselective desymmetrizations ties up with the necessity for a lengthy follow-up chemistry in order to arrive at the desired complex target structures.

As part of our recent activities towards streamlined implementations of desymmetrizative biocatalysis in a synthetic-organic setting exploiting skeletal rearrangements as means for the direct creation of molecular complexity,[4] we became interested in onium ylides as potential intermediates in such a chemoenzymatic scenario. Sigmatropic skeletal rearrangements represent a very powerful tool when it comes to C-C-coupling reactions with a high degree of stereochemical control in the construction of multiple chirogenic centers and particularly onium ylide rearrangements have found many applications in complex organic synthesis in recent years.[5] Depending on the nature of the onium ylides, the generation of these zwitterionic reactive species can sometimes be achieved simply by deprotonation of preformed ammonium or sulfonium salts (Scheme 1, top).[6] In this work, however, we focussed on oxonium ylides as reactive intermediates which are generally inaccessible via deprotonation pathways. Based on the early work by Kirmse, the most frequently employed approach towards these oxygen-centred betaines relies on the metal-catalyzed decomposition of diazomethane or substituted diazo compounds in presence of ethers as nucleophilic counterpart (Scheme 1, bottom).[7,8]



Scheme 1. Formation and rearrangement of onium ylides via deprotonation or diazomethane decomposition.

With an impressive history of applications of oxonium ylide shift reactions in total synthesis,[9] and the development of powerful catalyst families and asymmetric ligand-controlled protocols,[10] we envisioned that the Kirmse-Doyle rearrangement could act as an exquisite module in the context of chemoenzymatic synthesis strategies. Particularly, with regard to the direct structural relationship of Kirmse-Doyle-relevant diazoketones and carboxylic acids, as exemplified in countless instances as part of the Arndt-Eistert homologation, our design aimed to link an enzymatic synthesis of carboxylic acids by ester hydrolases with a metal-mediated rearrangement reaction (Scheme 2). More specifically, our strategy relied on an



Scheme 2. Chemoenzymatic strategy for the stereocontrolled assembly of complex, orthogonally functionalized tetrahydrofuranes.

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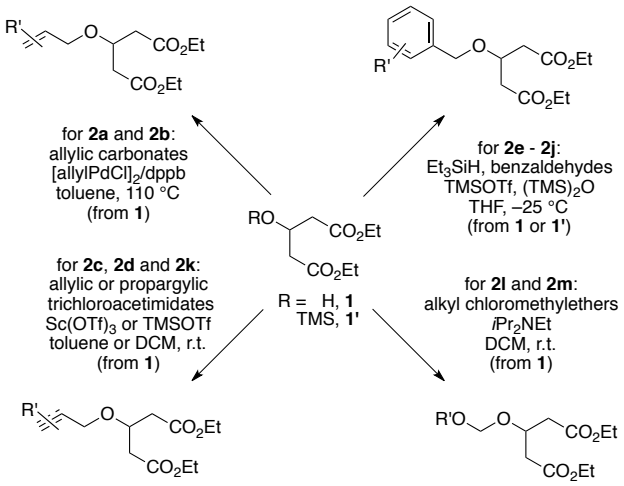
enantioselective desymmetrization of ether-functionalized glutarate diesters as substrates for lipase biocatalysts that would be followed by conversion of the liberated carboxylic acids into the corresponding diazoketones and their immediate copper- or rhodium-catalyzed intramolecular oxonium ylide rearrangement. As illustrated in scheme 2, this combination of a chirality-creating and a complexity-creating reaction step offers a rapid access to densely decorated and orthogonally functionalized O-heterocycles with high control over multiple stereogenic elements. Taking advantage of the unrivalled selectivities of enzymatic catalysts, this method is thereby complementing the modern synthetic toolbox for the stereoselective cyclization to tetrahydrofuranones relying on e.g. oxidative furan rearrangements,[11] radical hydroacylations,[12] or propargyl benzoate cycloisomerizations.[13]

Herein, we provide a detailed account on of our efforts to develop this chemoenzymatic approach utilizing various functionalized symmetric glutarates. On the basis of our preliminary results focusing on benzyl shift rearrangements,[14] this report puts emphasis on the synthetically even more appealing [2,3]-sigmatropic oxonium ylide chemistry for the synthesis of alkene and allene-substituted tetrahydrofurans and its application in streamlined strategies towards complex heterocyclic building blocks with full control over multiple stereogenic centers.

Results and Discussion

In order to conduct an extensive study on various glutarates bearing a series of different migrating groups for the oxonium ylide rearrangement, our initial focus was placed on the development of robust methods for the preparation of the symmetric starting materials. While the most obvious approach via Williamson etherification between 3-hydroxyglutarate and the suitable alkyl halides proved to be ineffective in most cases, a number of alternative methods based on previously described etherification protocols have been applied (Scheme 3). For the synthesis of *O*-allylated derivatives two protocols were successfully adapted. On one side, a palladium-catalyzed allylation using allylic carbonates under virtually base-free conditions yielded the allylated (**2a**, 95%) and cinnamylated glutarates (**2b**, 75%).[15] Since prenylation of **1** by the Tsuji-Trost protocol failed, an alternative Schmidt etherification by prenyl trichloroacetimidate was employed, and scandium triflate-catalyzed C-O bond formation resulted in a mixture of prenylated and reversely prenylated glutarates (66%, **2c**:**2d** = 64:36).[16] The challenging separation of both regioisomers was achieved by the dry column vacuum chromatography introduced by Harwood and Petersen.[17] Under similar conditions (butynyl trichloroacetimidate, TMSOTf, DCM, r.t.), propargylation yielded **2k** in 60%.[18] As already disclosed in our previous communication,[14] benzylic ethers were accessible via a Lewis acid-mediated, reductive etherification to give rise to **2e** - **2j** in moderate to good yields (46-82%). Finally, two alkoxymethyl ethers were synthesized by treatment of alcohol **1** with the respective alkoxymethyl chlorides and Hünig's base (**2l**, 60%; **2m**, 64%).



Scheme 3. Synthesis of 3-alkoxy-substituted diethyl glutarates.

With a diverse set of symmetric glutarate ethers in hand, the enzyme-catalyzed desymmetrization was surveyed. From a number of lipases and proteases tested for the enantioselective hydrolysis of allyl ether **2a,** lipase B from *Candida antarctica* stood out as a highly selective biocatalyst. Best results were obtained using an aqueous solution of CALB (**3a**, 99%, 96% *ee*) rather than the commonly employed immobilized form (**3a**, 90%, 81% *ee*). Moreover, we were delighted to see that under these conditions, nearly all of the tested glutarates were smoothly desymmetrized with high yields and generally excellent optical purities (≥96% *ee*) (Scheme 4). As an exception, the reversely prenylated diester **2d** reacted sluggishly and in addition to a low yield of 52% after an extended reaction period of seven days, (*S*)-**3d** was isolated with a mediocre enantiomeric excess of 26%. A switch in enantioselectivity was observed replacing the lipase catalyst by the protease α-chymotrypsin that allowed also the preparation of (*R*)-configured **3a** in high yield and good enantiopurity, providing the flexibility required from a generally applicable synthetic methodology.

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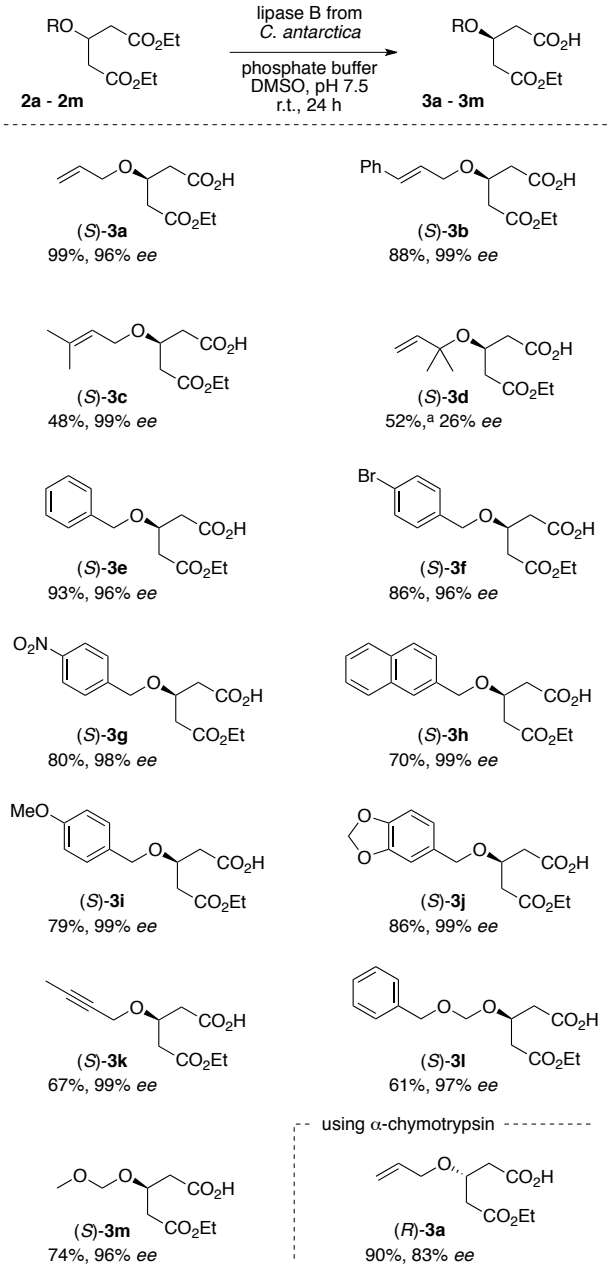
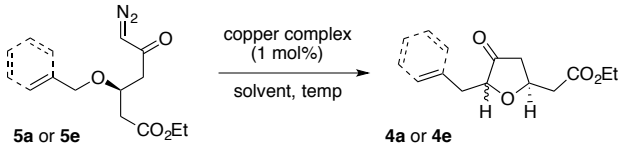


Scheme 4. Enantioselective desymmetrization of glutarates. [a] after 7 days.

From the collection of optically pure glutaric monoesters, allyl ether **3a** and benzyl ether **3e** were chosen for the investigation and optimization of the planned activation-rearrangement sequences as model substrates for the [2,3]-sigmatropic allyl migration and the [1,2]-Stevens shift, respectively. Therefore, the corresponding diazoketones **5a** and **5e** were synthesized and isolated using the previously identified optimized protocol via a sequence of chlorination (oxalyl chloride) and diazomethylation (diazomethane + CaO).[19] Numerous complexes of various transition metals have been tested for the selective decomposition of either diazoketone, but solely complexes based on copper and rhodium gave a positive outcome. Interestingly, there was a very distinct difference between the two reaction pathways and their respective, most appropriate metal catalysts. A broad screening of Cu(II) and Cu(I) complexes revealed that the very commonly employed acetylacetonate catalyzed the [2,3]-sigmatropic rearrangement to **4a** in good yield and high *trans* diastereoselectivity while the same complex failed to provide any conversion in the related [1,2]-benzyl shift (Table 1, entries 1-3). Contrarily, $[Cu(MeCN)_4BF_4]$ catalysis gave the Stevens product **4e** in 54% yield but proved to be unproductive in the Kirmse-type reaction (Table 1, entry 5). Most stunningly, variation of the counterion (BF_4^- to TfO^- or PF_6^-) not only rendered a Kirmse-active system (Table 1, entry 6 & 7), but after slight optimization of the solvent system and minor temperature adjustments, a highly efficient and perfectly *trans*-selective catalytic rearrangement protocol was obtained, yielding the desired allylated tetrahydrofuranone **4a** in 96%yield and 99% diastereomeric excess (Table 1, entry 9).

Table 1. Screening of copper complexes for the [1,2]-Stevens shift and [2,3]-sigmatropic rearrangement of glutarate-derived diazoketones.[a]



Entry	copper source	solvent	temp [°C]	"Kirmse" **5a** to **4a**	"Stevens" **5e** to **4e** [b]
1	$Cu(acac)_2$	DCM	23	90% 92% *trans*	no conversion
2	$Cu(hfacac)_2$	DCM	23	16% 62% *trans*	complex mixture
3	$Cu(tfacac)_2$	DCM	23	28% 82% *trans*	complex mixture
4	CuOAc	DCM	23	48% 86% *trans*	n.d.
5	$[Cu(MeCN)_4]BF_4$	DCM	23	5% 97% *trans*	54% 72% *trans*
6	$[Cu(MeCN)_4]OTf$	DCM	23	55% 91% *trans*	n.d.
7	$[Cu(MeCN)_4]PF_6$	DCM	23	90% 99% *trans*	50% 72% *trans*
8	$[Cu(MeCN)_4]PF_6$	DCM	0	95% 99% *trans*	n.d.
9	**$[Cu(MeCN)_4]PF_6$**	**DCE**	**0**	**96%** **99% *trans***	n.d.
10	$[Cu(MeCN)_4]PF_6$	DCE	–78	63% 99% *trans*	n.d.
11	$[Cu(MeCN)_4]PF_6$	$CHCl_3$	0	38% 91% *trans*	n.d.
12	$[Cu(MeCN)_4]PF_6$	benzene	0	38% 99% *trans*	n.d.
13	$[Cu(MeCN)_4]PF_6$	THF	0	30% 98% *trans*	n.d.

[a] Reaction conditions: **5a** or **5e** (0.2 mmol) and copper complex (2 μmol). in 20 mL of solvent. Yields and selectivities were determined by ^{1}H-NMR using anisol as a standard. Abbreviations: acac = acetylacetonate; hfacac = 1,1,1,5,5,5-hexafluoroacetylacetonate; tfacac = 1,1,1-trifluoroacetylacetonate. [b] 5 mol% catalyst were used.

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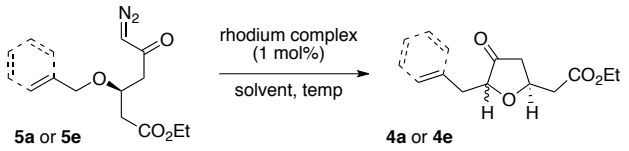
As none of the tested copper complexes met our requirements for a selective [1,2]-benzyl shift, another catalyst test was conducted, now investigating different dimeric rhodium carboxylates. Firstly, although good to excellent yields were obtained for the rearrangement of **4a**, the induced diastereoselectivities using rhodium complexes fell short in comparison to the [Cu(MeCN)$_4$PF$_6$]-catalyzed procedure. Regarding the unsolved Stevens rearrangement challenge, both rhodium triphenylacetate and the Rh$_2$esp$_2$ complex gave rise to **4e** in high yields, however, almost statistic mixtures of both diastereomers were observed (Table 2, entry 1 & 2). The corresponding trifluoroacetate on the other hand failed to yield any of the *C*-benzylated product (Table 2, entry 3). Improved inductions were observed using electronically and sterically unbiased rhodium acetate and octanoate (Table 2, entry 5 & 6) giving rise to the desired Stevens-product in acceptable yield and selectivity. Efforts to further enhance the *trans*-preference by temperature and solvent adjustments failed (Table 2, entries 6-9). Also, the attempt to reverse the selectivity in favor of the *cis*-product, by exploiting a ligand-controlled approach, was not pursued in much detail after literally no matched/mismatched situation was observed employing enantiomeric proline-based rhodium complexes (Table 2, entry 10 & 11). The lack of a clear correlation between steric or electronic catalyst properties and the induced diastereoselectivity remains puzzling and underlines the necessity for a more systematic mechanistic study to shed light on factors such as the involvement of metal-associated ylides vs. 'metal-free' betaines, or the nature of the [1,2]-transposition itself.[5a,10b] All tested benzylic substrates followed a similar trend and the tetrahydrofuranones **4e** - **4j** were obtained in *trans*-selectivities up to 88% (see Supporting Information).[11]

Table 2. Screening of rhodium complexes for the [1,2]-Stevens shift and [2,3]-sigmatropic rearrangement of glutarate-derived diazoketones.

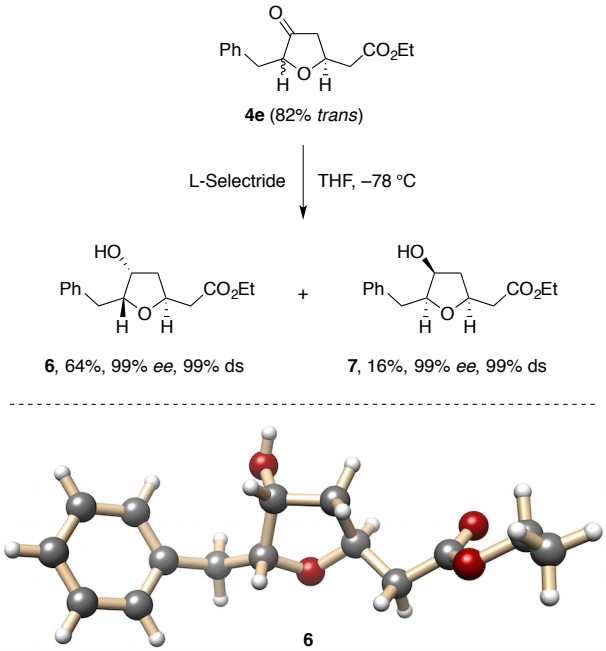


5a or **5e** → **4a** or **4e**

Entry	rhodium source	solvent	temp [°C]	"Kirmse" **5a** to **4a**	"Stevens" **5e** to **4e**
1	Rh$_2$(tpa)$_4$	DCM	0	97% 53% *cis*	81% 55% *trans*
2	Rh$_2$(esp)$_2$	DCM	0	92% 73% *trans*	92% 69% *trans*
3	Rh$_2$(tfa)$_4$	DCM	0	81% 59% *trans*	no conversion
4	Rh$_2$(OAc)$_4$	DCM	0	94% 79% dr	80% 80% *trans*
5	**Rh$_2$(oct)$_4$**	**DCM**	**0**	70% 82% dr	**79%** **82% *trans***
6	Rh$_2$(oct)$_4$	DCM	–78	n.d.	36% 81% *trans*
7	Rh$_2$(oct)$_4$	DCM	40	n.d.	42% 82% *trans*
8	Rh$_2$(oct)$_4$	benzene	0	n.d.	68% 70% *trans*
9	Rh$_2$(oct)$_4$	THF	0	n.d.	28% 83% *trans*
10	Rh$_2$((*R*)-dosp)$_4$	DCM	0	63% 74% *trans*	80% 80% *trans*
11	Rh$_2$((*S*)-dosp)$_4$	DCM	0	84% 63% *trans*	83% 79% *trans*

[a] Reaction conditions: **5a** or **5e** (0.2 mmol) and rhodium complex (2 μmol). in 20 mL of solvent. Yields and selectivities were determined by ^{1}H-NMR using anisol as a standard. Abbreviations: tpa = triphenylacetate; esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionate; tfa = trifluoroacetate, oct = octanoate; dosp = *N*-(4-dodecylphenylsulfonyl)prolinate.

The major issue with the moderate induction under the optimized conditions for the Stevens-type rearrangement (Rh$_2$(oct)$_4$, DCM, 0 °C) was the fact that the two diastereomers could not be separated chromatographically on a preparative scale. However, after treatment of the obtained *cis*/*trans*-mixture of tetrahydrofuranone **4e** with L-Selectride at low temperature, two epimeric alcohols could be separated and isolated in stereochemically pure form (Scheme 5). The major isomer **6** was crystallized and X-ray crystal structure analysis unambiguously confirmed the anticipated connectivity and relative stereochemistry resulting from the previous oxonium ylide rearrangement step (see Supporting Information for ORTEP and crystallographic data). The thus obtained alcohols can on one side be used as functional building blocks towards more complex heterocyclic targets,[14] but could also act as precursors for 2,5-disubstituted tetrahydrofurans through Barton-McCombie deoxygenation.[20,21]



Scheme 5. Diastereoselective reduction of *C*-benzylated tetrahydrofuranone **4e**, and X-ray crystal structure of the major isomer **6**.

In contrast to the moderate diastereocontrol in the rearrangement of simple diazoketones (such as **5e**) derived from diazomethane, a related stabilized α-diazo-β-ketoester exhibited much higher selectivity. Here, the three-step cascade consisting of (i) of activation of the previously desymmetrized acid **3e**, (ii) acid chloride trapping by ethyl diazoacetate, and (iii) decomposition of the diazoketoester gave rise to the stereochemically pure tetrahydrofuranone **8** (Scheme 6). Unfortunately,

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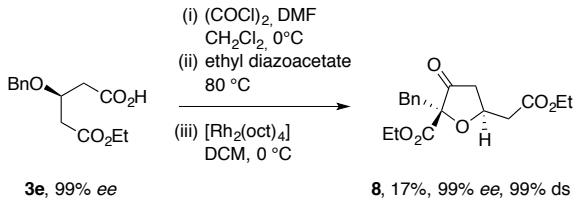
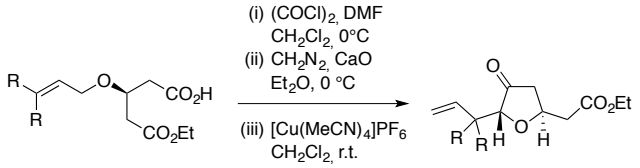
the very high diastereomeric excess of the product was accompanied by a rather low overall yield of 17% which seemed surprising since no particularly low rates or significant side product formation could be observed in the decomposition of the diazoketoester.



3e, 99% *ee* **8**, 17%, 99% *ee*, 99% ds

Scheme 6. Formation and rearrangement of a glutarate-derived α-diazo-β-ketoester.

Due to the apparent benefit of excellent selectivities in the [2,3]-sigmatropic oxonium ylide rearrangement, and the flexibility of allylic groups to act as versatile functional handle for numerous subsequent synthetic transformations, our particular focus was put on the in-depth study of the copper-mediated Kirmse-Doyle-type reaction. Initial experiments focused on the [2,3]-sigmatropic rearrangement of oxonium ylides bearing symmetrically terminated olefins that would allow the investigation of the induced diastereoselectivity of the Cu-catalyzed system. While already the formation of a diazoketone from the reversely prenylated glutarate **3d** failed, both the plain allyl ether **3a** and the prenyl derivative **3c** were cleanly activated in a two-step fashion using oxalyl chloride and etheral diazomethane, whereupon treatment with 5 mol% of $[Cu(MeCN)_4PF_6]$ resulted in the production of the allylated tetrahydrofuranones **4a** and **4c** in 72% and 45%, respectively (Scheme 7). In addition to a perfect induced selectivity in favor of the *trans*-isomer, the specific formation of the reversely *C*-prenylated **4c** underlines the truly sigmatropic character of the transformation in preference over alternative feasible fragmentation-recombination pathways.[22]

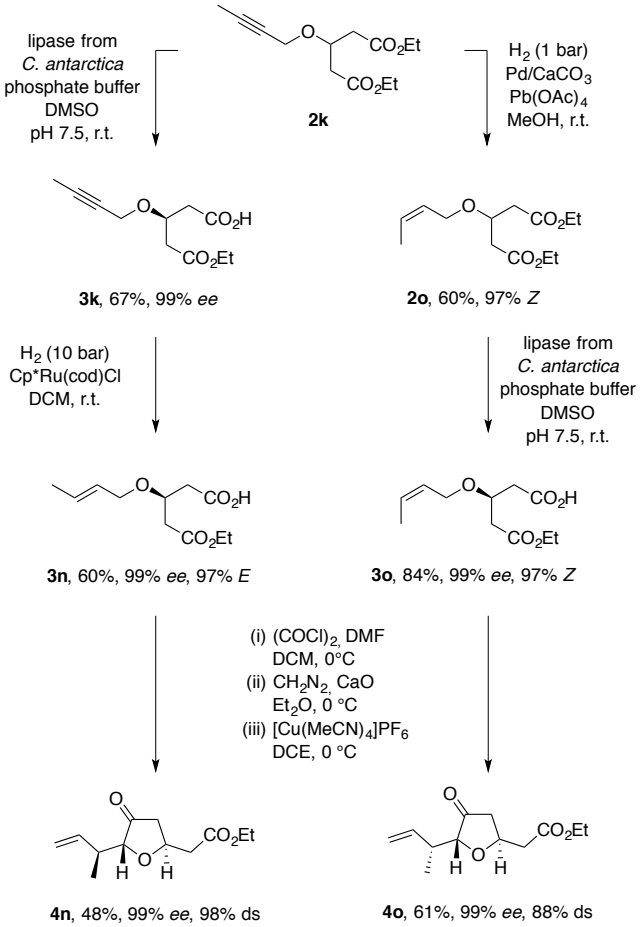


R = H: **3a**, 96% *ee*
Me: **3c**, 99% *ee*

R = H: **4a**, 72%, 96% *ee*, 99% ds
Me: **4c**, 45%, 99% *ee*, 99% ds

Scheme 7. Induced diastereoselectivity in the Kirmse-Doyle-type rearrangement of symmetrically terminated allylic ethers.

With the incorporation of unsymmetric allylic fragments in the rearrangement scenario (*E*- or *Z*-configured 3-substituted allyl ethers) a further increase of molecular complexity can be attained as a selective C-C-bond forming process would result in the controlled introduction of a third stereogenic, exocyclic center. Starting from the symmetric propargylic ether **2k**, a sequence consisting of a metal-catalyzed selective alkyne reduction and the previously disclosed lipase-mediated desymmetrization should give access to either *E*- or *Z*-crotyl ethers **3n** or **3o** in optically pure form. Interestingly, here the order of events proved to be pivotal to achieve high selectivities for the desired stereoisomers. Crotyl ether **3n** was obtained in 99% *ee* and 97% *E*-configuration after enzymatic desymmetrization followed by Fürstner's *E*-selective hydrogenation protocol using Cp*Ru(cod)Cl as catalyst.[23] In contrast to the high *E*-preference in the reduction of monoester **3k**, the very same procedure applied on diester **2k** yielded a mixture of isomers (*E*/*Z* = 87/13). For the preparation of the *Z*-crotyl substituted monoester **3o**, best results were obtained when the reduction (Lindlar hydrogenation, $Pd/CaCO_3$, $Pb(OAc)_4$) was performed prior to the actual desymmetrization. Here, also monoester **3o** was isolated in 99% *ee* and 97% *Z*-selectivity over two steps. Attempts to perform the alternative Lindlar hydrogenation of the propargylic monoester **3k** remained fruitless. With both *E*- and *Z*-olefins in hand, the activation-rearrangement sequence was tested. To our delight, the formation of the **3n**-derived diazoketone and its copper-catalyzed decomposition proceeded smoothly and the desired tetrahydrofuranone **4n** was isolated with a high degree of diastereoselectivity. Comparative NMR- and GC-studies of the product with mixtures obtained from less selective catalysts (e.g. Rh_2tfa_4) revealed that out of the four possible stereoisomers only one pair was formed which was assigned to the two epimers differing from each other at the exogenic center (**4n**:**4o** = 98:2). Moreover, also the rearrangement of the *Z*-derivative **3o** showed an optimal induced *trans*-selectivity and, as anticipated, the opposite preference regarding the configuration at the exocyclic center was observed (**4o**:**4n** = 88:12).



Scheme 8. Highly enantio- and diastereocontrolled synthesis of tetrahydrofuranones bearing three stereogenic centers.

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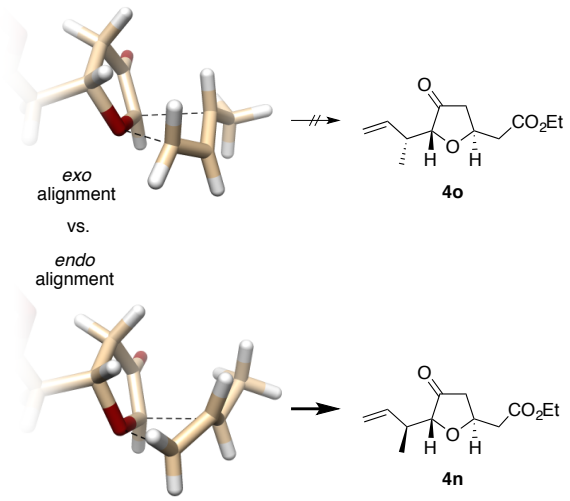
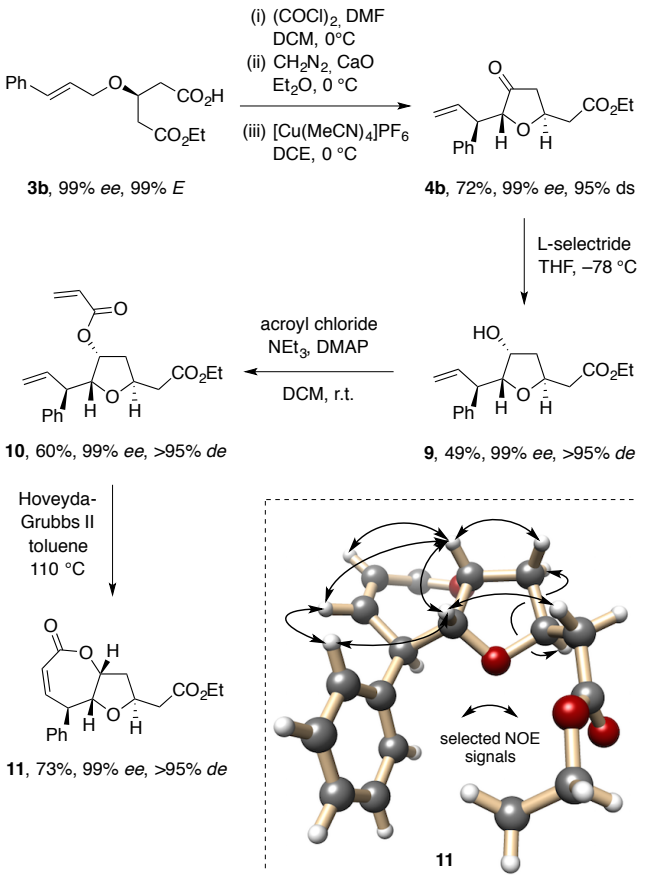
The perfect induced diastereoselectivity can easily be explained by the preferred formation of a *trans*-configured oxonium ylide due to the steric bias caused by ethoxyacetyl substituent at the existing stereogenic center. Under the assumption of a prevailing *trans*-arrangement, the migration of crotyl-derived onium ylides can occur via two distinct orientations of the allylic fragment relative to the newly formed *O*-heterocyclic system. The preference for either *exo*- or *endo*-alignment dictating the simple diastereoselectivity can serve to explain the stereochemical outcome regarding the exocyclic chirogenic element (Scheme 9). As illustrated for the rearrangement of an *E*-configured *O*-crotyl oxonium ylide, the $[Cu(MeCN)_4PF_6]$-induced transformation obviously proceeded via the *endo*-alignment in >99% selectivity, considering the imperfect *E*-selectivity in the preceding alkyne reduction, from where the observed major isomer **4n** is formed. Likewise, the rearrangement of the *Z*-configured crotyl species occurred with *endo*-preference too, although the apparent selectivity for the tetrahydrofuran **4o** remained slightly lower. While we are unable to provide a clear rational for this stereochemical feature at the moment, we are aiming to address this open mechanistic question in a focussed study combining experimental and computational techniques.



Scheme 9. Illustration of potential alignments in the diastereoselective formation of exocyclic stereogenic centers in the rearrangement of crotyl ethers.

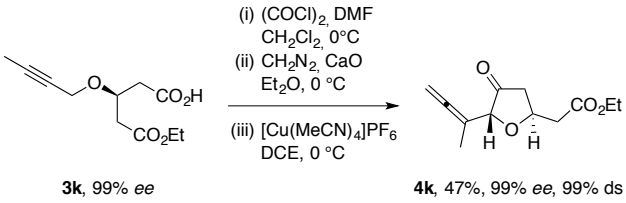
The same trend was also observed in the rearrangement of cinnamyl ether **3b**. Activation and [2,3]-sigmatropic allyl shift of the enantio- and diastereomerically pure glutaric monoester occurred with high yield and gave rise to the tetrahydrofuranone **4b** in 90% diastereomeric excess. The stereopurity could be further enhanced after chromatographic purification of the corresponding alcohol **9** that was obtained by selective reduction using L-Selectride. Subsequent esterification by acryloyl chloride and ruthenium-catalyzed ring closing olefin metathesis yielded the bicyclic derivative **11**. Both spectroscopic and crystallographic methods were used to thoroughly analyse the final product of the sequence that helped to unequivocally confirm the anticipated induced and simple diastereoselectivity in the involved [2,3]-sigmatropic rearrangement (see Supporting Information for ORTEP and crystallographic data).[24]

Furthermore, this reaction cascade also highlights the synthetic potential of the presented chemoenzymatic approach as tool in heterocyclic chemistry providing excellent control over multiple stereocenters and rapid amplification of molecular complexity.



Scheme 10. Rearrangement of a glutarate-derived cinnamyl ether and subsequent synthesis of the bicyclic **11** via ring-closing metathesis.

The use of propargylic ethers in the desymmetrization/ rearrangement strategy represents a highly interesting extension of the concept, as the [2,3]-sigmatropic shift would render heterocyclic products with allenic side chains as additional functional moiety that provide an additional set of allene-specific follow-up reactions.[25] Gratifyingly, not only the desymmetrization by CALB yielded **3k** in high enantiomeric excess, but also the activation-rearrangement protocol proceeded smoothly giving rise to the allenic tetrahydrofuranone **4k** in enantio- and diastereomerically pure form (Scheme 11).



Scheme 11. Allene synthesis based on the [2,3]-sigmatropic oxonium ylide rearrangement.

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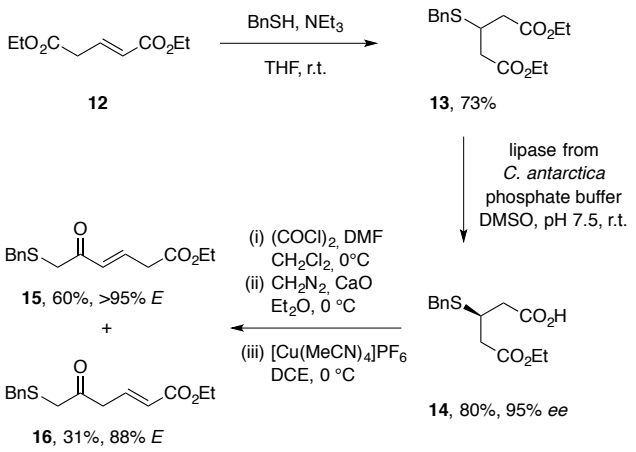
The broad success of the presented chemoenzymatic strategy prompted us to try to expand our studies to other onium-generating substrates. Unfortunately, all efforts to engage alkoxyalkyl ethers like **3l** and **3m** in the desired rearrangement chemistry failed and produced complex mixtures of non-cyclized side products. A more selective, even if not anticipated, pathway was observed when a structurally related sulfur-derivative was subjected to the reaction cascade. Here, the benzyl thioether **13** was synthesized in good yield via thia-Michael addition to diethyl glutaconate (**12**) and subsequent enantioselective enzymatic hydrolysis gave access to monoester **14** in 95% *ee*. Applying the identical activation protocol as for the etheral substrates, decomposition of the intermediate diazoketone resulted in the formation of two distinct olefinic products (**15** and **16**) in high overall yield and with good to excellent selectivity in favor of the *E*-configured C-C double bonds (Scheme 12). Apparently, after formation of the sulfonium ylide, a Hofmann-type elimination pathway prevails over the expected benzyl shift, where the differences in flexibility for the elimination of exo- and endocyclic protons likely account for the superior stereoselectivity observed in the formation of enone **15** in comparison to enoate **16**.



Scheme 12. Unexpected Hofmann-type elimination of a 3-mercaptoglutarate-derived sulfonium ylide.

Conclusions

In summary, we were able to successfully construct a novel chemoenzymatic approach yielding functionalized tetrahydrofurans with excellent control over enantio- and diastereoselectivity. Here, the combination of a broadly applicable biocatalytic desymmetrization of ether-functionalized glutarates with the copper-mediated [2,3]-sigmatropic rearrangement provides a concise access to the O-heterocyclic building blocks bearing allylic and allenylic moieties. The resulting pattern of functional groups that can be modified in a highly orthogonal manner allows for a rich follow-up chemistry with great perspectives to implement the strategy in more complex synthetic scenarios.

Experimental Section

General remarks: All reactions carried out under argon atmosphere were performed with dry solvents using anhydrous conditions in flame-dried glassware, unless otherwise stated. pH-stat titrations were run on a Titroline alpha plus (SI Analytics). All products were purified by column chromatography over silica gel (Macherey-Nagel MN-Kieselgel 60 (40-60 µm, 240−400 mesh)). Dry vaccum chromatography was performed with Macherey-Nagel MN-Kieselgel 60 (15-40 µm, 400−800 mesh). Reactions were monitored by thin layer chromatography (TLC) carried out on Macherey-Nagel pre-coated silica gel plates (TLC Silica gel 60 F_{254}) using UV light as the visualizing agent and Hanessian stain as developing agent. ^{1}H- and ^{13}C-NMR-spectra were recorded on Bruker AV-600, AV-500 and AV-300 instruments at room temperature. Chemical shifts are reported in parts per million (ppm) calibrated using residual non-deuterated solvent as internal reference ($CHCl_3$ at 7.26 ppm (^{1}H-NMR) & 77.16 ppm (^{13}C-NMR)). Infrared-spectra were recorded on a Shimadzu IRAffinity-1 FT-IR-spectrometer, absorption bands are reported in wave numbers [cm^{-1}]. High resolution mass spectrometry was performed on a Finnigan *MAT 900 S* by electrospray ionization. For standard resolution either Agilent LC/MSD VL with electron spray ionization or an Agilent GC-System 8940A with a mass detector 5975 employing helium as carrier gas was used. Chiral gas chromatography was coducted on a Hewlett Packard HP 6890 system with an Agilent 6890 series injector on a Lipodex E column (25 m x 0.25 mm, 0.25 µm) using flame ionisation dectection. Hydrogen (from a Domnick Hunter 20H H_2-generator) was used as carrier. High performance liquid chromatography was performed on a Merck Hitachi L-7250 with a Merck L-7455 detector and Merck column oven L-7360 (18 °C) using analytical Daicel AD-H/OD-H columns (250 mm x 4.6 mm). Optical rotations were measured on a Perkin-Elmer 343plus. X-Ray crystal structure analysis was conducted using a Bruker D8 Venture equipped with a copper micro focus source and Photon 100 detector. The analysis program used was Apex 3. The structures were solved with Shelxt and refined using the program Shelxl. Commercially available reagents were used without further purification. Dry dichloromethane was freshly distilled from calcium hydride. Anhydrous tetrahydrofuran and toluene was freshly distilled from sodium/benzophenone, Anhydrous dichloroethane was obtained from Sigma-Aldrich. The copper and rhodium complexes were purchased from Sigma-Aldrich and Strem. Lipase B from *C. antarctica* was obtained as aqueous solution from Sigma-Aldrich (L3170). Etheral diazomethane was synthesized from N-methyl-N-nitrosourea.[26] Caution: Diazomethane is toxic and potentially explosive. All operation involving this reagent must be carried out in a well-ventilated hood wearing heavy gloves and googles. The work must be conducted behind an adequate safety screen, ground joints and sharp surfaces should be avoided.

Representative procedure for the enantioselective enzymatic desymmetrization: Diethyl 3-allyloxyglutarate (**2a**, 5.0 g, 20.5 mmol) was dissolved in phosphate buffer (250 mL, 0.1 M, pH 7.5, 20% DMSO) connected to a pH-stat titrator (SI Analytics, Titroline alpha plus). After initiation of the reaction by addition of a solution of lipase B from *Candida antarctica* (250 µL, *Sigma L3170*), the mixture was stirred at room temperature and the pH was kept constant by automatic addition of aqueous NaOH (1 M). After 24 h, aqueous HCl (1 M, 25 mL) was added, the solution was extracted with diethyl ether (3x 50 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the crude carboxylic acid was purified by column chromatography (SiO_2, mixtures of cyclohexane and diethyl ether + 1% AcOH). **3a** (4.39 g, 20.3 mmol, 99%, 96% *ee*) was obtained as colorless liquid. R_f (cyclohexane/ethyl acetate/acetic acid 70/29/1) = 0.40. $[\alpha]_D^{20}$ (c 1.07, $CHCl_3$) = +1.32. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.87 (ddt, ^3J = 17.2 Hz, ^3J = 10.4 Hz, ^3J = 5.7 Hz, 1H), 5.26 (ddt, ^3J = 17.2 Hz, ^2J = 1.1 Hz, ^4J = 1.6 Hz, 1H), 5.16 (ddt, ^3J = 10.4 Hz, ^2J = 1.1 Hz, ^4J = 1.6 Hz, 1H), 4.22 (dddd, ^3J = 6.7 Hz, ^3J = 6.5 Hz, ^3J = 6.0 Hz, ^3J = 5.8 Hz, 1H), 4.14 (q, ^3J = 7.1 Hz, 2H), 4.07 (dd, ^3J = 5.7 Hz, ^4J = 1.6 Hz, 2H), 2.68 (dd, ^2J = 15.9 Hz, ^3J = 6.5 Hz, 1H), 2.65 (dd, ^2J = 15.6 Hz, ^3J = 6.7 Hz, 1H) 2.64 (dd, ^2J = 15.9 Hz, ^3J = 5.8 Hz, 1H), 2.62 (dd, ^2J = 15.6 Hz, ^3J = 6.0 Hz, 1H), 1.26 (t, ^3J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 176.7 (s), 171.0 (s), 134.5 (d), 117.5 (t), 72.2 (d), 71.2 (d), 60.9 (t), 39.6 (t), 39.5 (t), 14.3 (q). IR (ATR): ν [cm^{-1}] = 3669 (w), 3174 (br, w), 2986 (m), 2901 (m), 1732 (s), 1709 (s), 1375 (m), 1194 (m), 1074 (s). Elemental analysis calcd (%) for $C_{10}H_{16}O_5$: C 55.55, H 7.46; found: C 55.18, H 7.43.

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Representative procedure for the synthesis of diazoketones: Under argon, monoester **3a** (649 mg, 3.0 mmol) was dissolved in dry dichloromethane (15 mL) and cooled to 0 °C. Dry DMF (15 mL) and oxalyl chloride (1.14 g, 9.0 mmol) were added, and the reaction progress was monitored by IR spectrometry. After 2 h, all volatiles were removed in vacuo and the residue was redissolved in dry dichloromethane (3 mL). The solution of the acid chloride was added dropwise at 0 °C to a mixture of CaO (1.68 g, 30.0 mmol) and diazomethane (0.4 M in Et_2O, 75 mL, 30 mmol). After 15 min, argon was purged through the resulting suspension (10 min) to remove excess CH_2N_2. Afterwards, the mixture was filtered over Celite, the filtrate was washed with aqueous bicarbonate (saturated, 50 mL) and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. After purification by column chromatography (SiO_2, cyclohexane/ethyl acetate/triethylamine 90/9/1), diazoketone **5a** (505 mg, 2.10 mmol, 70%) was obtained as yellow liquid. R_f (cyclohexane/ethyl acetate 6/4) = 0.45. $[\alpha]_D^{20}$ (c 1.09, $CHCl_3$) = 18.3. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.90-5.80 (m, 1H), 5.34 (s, 1H), 5.24 (dddd, ^3J = 17.2 Hz, ^4J = 3.2 Hz, ^3J = 1.6 Hz, ^4J = 1.1 Hz, 1H), 5.14 (dddd, ^3J = 10.4 Hz, ^4J = 2.6 Hz, ^2J = 1.6 Hz, ^4J = 1.1 Hz, 1H), 4.23 (m, 1H, H-5), 4.13 (q, ^3J = 7.1 Hz, 2H), 4.05-4.01 (m, 2H), 2.65-2.50 (m, 4H), 1.24 (t, ^3J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.3 (s), 171.0 (s), 134.6 (d), 117.3 (t), 72.8 (d), 71.1 (t), 60.7 (t), 55.8 (d), 45.8 (t), 39.7 (t), 14.3 (q). IR (ATR): ν [cm^{-1}] = 3090 (w), 2936 (w), 2100 (s), 1730 (s), 1634 (s), 1368 (s), 1350 (s), 1072 (s). ESI-HRMS calcd for $C_{11}H_{16}N_2O_4Na$ $[M+Na]^+$: 263.1008; found: 263.1007.

Representative procedure for the [2,3]-sigmatropic oxonium ylide rearrangement: Diazoketone **5a** (48 mg, 200 μmol) was dissolved in 1,2-dichloroethane (19 mL). At 0 °C, $[Cu(MeCN)_4]PF_6$ (1 mg, 2 μmol) in 1,2-dichloroethane (1 mL) was added and the reaction mixture was stirred at 0 °C for 60 min. The solution was washed with aqueous Na_2EDTA (0.4 M, 50 mL) and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, cyclohexane/diethyl ether 95/5 to 8/2) and **4a** (39 mg, 0.19 mmol, 93 %, 99.5 % *trans*) was obtained as colorless liquid. R_f (cyclohexane/ethyl acetate 7/3) = 0.48. $[\alpha]_D^{20}$ (c 0.74, $CHCl_3$) = +64.4. *Major diastereomer*: ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.80 (ddt, ^3J = 17.2 Hz, ^3J = 10.1 Hz, ^3J = 7.1 Hz, 1H), 5.14 (dd, ^3J = 17.2 Hz, ^2J = 1.5 Hz, 1H), 5.11 (dd, ^3J = 10.1 Hz, ^2J = 1.5 Hz, 1H), 4.76 (dddd, ^3J = 7.2 Hz, ^3J = 6.8 Hz, ^3J = 6.5 Hz, ^3J = 6.0 Hz, 1H, H-5), 4.15 (q, $^3J_{2,1}$ = 7.1 Hz, 2H, H-2), 4.04 (dd, ^3J = 7.3 Hz, ^3J = 4.8 Hz, 1H), 2.75 (dd, ^2J = 16.0 Hz, ^3J = 6.0 Hz, 1H), 2.66 (dd, ^2J = 18.4 Hz, ^3J = 7.2 Hz, 1H), 2.61 (dd, ^2J = 16.0 Hz, ^3J = 6.8 Hz, 1H), 2.55-2.30 (m, 3H), 1.25 (t, ^3J = 7.1 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 201.6 (s), 171.0 (s), 134.7 (d), 117.4 (t), 71.1 (d), 68.9 (d), 60.8 (t), 39.8 (t), 39.4 (t), 39.2 (t), 14.3 (q). *Minor diastereomer* (selected signals): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.57-4.47 (m, 1H, H-5), 3.86 (dd, ^3J = 10.3 Hz, ^3J = 6.7 Hz, 1H), 2.83 (dd, ^2J = 15.9 Hz, ^3J = 6.1 Hz, 1H), 2.21 (dd, ^2J = 18.2 Hz, ^3J = 10.3 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.9 (s), 134.5 (d), 117.2 (t), 43.9 (t). IR (ATR): ν [cm^{-1}] = 2984 (w), 1798 (s), 1730 (s), 1167 (s), 1076 (m), 1026 (m). ESI-HRMS calcd for $C_{11}H_{16}O_4Na$ $[M+Na]^+$: 235.0941; found: 235.0942.

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Keywords: heterocycles • chemoenzymatic • lipase • sigmatropic • transition metal catalysis

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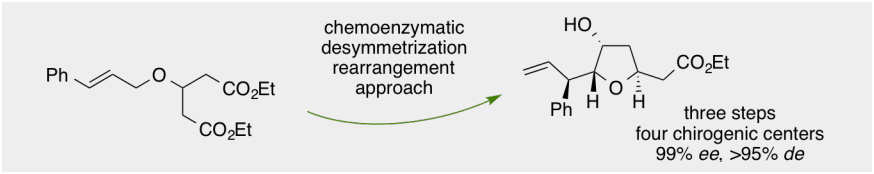

A novel chemoenzymatic cascade enables the preparation of densely decorated tetrahydrofuran building blocks. The direct combination of a lipase-catalyzed desymmetrization of 3-alkoxy-glutarates rendering highly enantioenriched carboxylic acid intermediates and the subsequent activation and copper-mediated oxonium ylide rearrangement furnishes stereodefined functionalized *O*-heterocycles. The two-step protocol offers a streamlined and flexible access to tetrahydrofuranones bearing unsaturated side chains with full control over multiple stereogenic centers.

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