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Oxonium Ylide Rearrangement of Enzymatically Desymmetrized Glutarates

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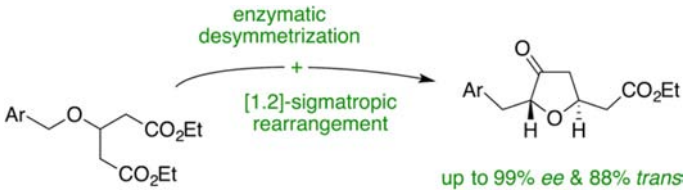
ABSTRACT

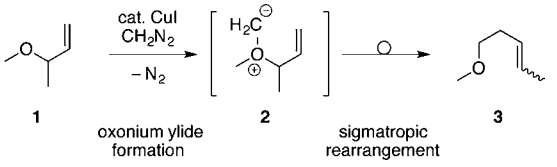


The combination of an enzyme-mediated enantioselective desymmetrization of readily available 3-benzyloxyglutarates and subsequent rhodium-catalyzed oxonium ylide rearrangement of their corresponding in situ derived diazo ketones offers a very concise and highly stereoselective access to functionalized tetrahydrofuranone building blocks.

The controlled migration of allylic and benzylic substituents within onium ylide structures has a long tradition as a tool in synthetic organic chemistry.[1] Starting with the observation by Stevens in the 1920s that *N*-benzylammonium salts, upon deprotonation, undergo [1,2]-benzyl shifts to yield *C*-benzylated products,[2] this chemistry has been extensively studied over the past decades and found various applications in the preparation of complex target structures.[3] While ammonium and sulfonium ylides are in many cases easily generated by proton abstraction from their respective onium halides,[3,4] the strongly alkylating properties of oxonium salts prohibited extension of this protocol to the corresponding oxygen centered transformations. With the report by Kirmse in 1968 (Scheme 1), describing the decomposition of diazomethane in the presence of allylic ethers (**1**) and a copper catalyst, oxonium ylide chemistry became feasible for the first time.[5]

Subsequently, the field of oxonium ylide rearrangements gradually came into focus in modern organic chemistry,[6]

Scheme 1. Kirmse's [2,3]-Sigmatropic Oxonium Ylide Rearrangement



and not surprisingly, thanks to the ability to quickly generate molecular complexity from well accessible carboxylic acid derivatives, these rearrangement reactions have in recent years also made their way into strategies for the total synthesis of structurally sophisticated natural products.[7]

Based on our recent studies on the implementation of biocatalytic desymmetrization reactions into synthetic strategies,[8] we envisaged that such a chemoenzymatic route was also applicable for the preparation of optically active precursors for the formation and rearrangement of functionalized

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(2) Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.* **1928**, 3193–3197.
(3) Review: Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043–1062.
(4) Reviews: (a) Clark, J. S., Ed. *Nitrogen, Oxygen and Sulfur Ylide Chemistry: A Practical Approach in Chemistry*; Oxford University Press: Oxford, 2002. (b) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341–2372.
(5) Kirmse, W.; Kapps, M. *Chem. Ber* **1968**, *101*, 994–1003.
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(7) Recent examples: (a) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem.* **2007**, *119*, 441–444. *Angew. Chem., Int. Ed.* **2007**, *46*, 437–440. (b) Clark, J. S.; Vignard, D.; Parkin, A. *Org. Lett.* **2011**, *13*, 3980–3983. (c) Hodgson, D. M.; Man, S. *Chem.—Eur. J.* **2011**, *17*, 9731–9737.
(8) (a) Thiel, D.; Deska, J. *Synlett* **2013**, *24*, 1529–1532. (b) Manzuna Sapu, C.; Deska, J. *Org. Biomol. Chem.* **2013**, *11*, 1376–1382. (c) Hammel, M.; Deska, J. *Synthesis* **2013**, *44*, 3789–3796. (d) Manzuna Sapu, C.; Bäckvall, J.-E.; Deska, J. *Angew. Chem.* **2011**, *123*, 9905–9908. *Angew. Chem., Int. Ed.* **2011**, *50*, 9731–9734.

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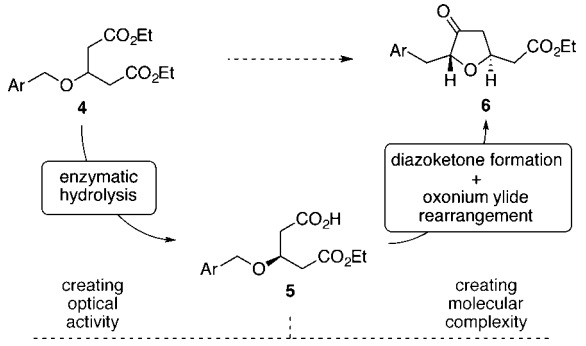
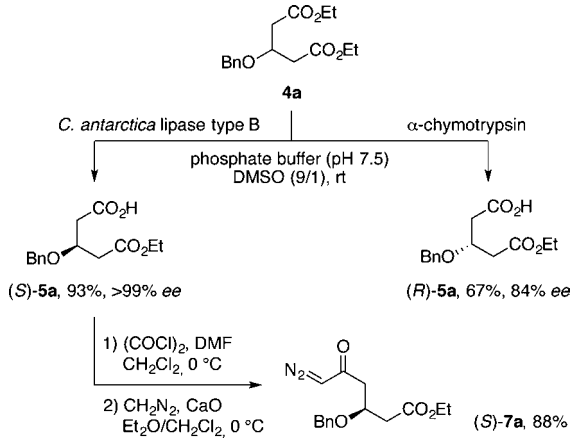
oxonium ylides. Prochiral glutarates and glutaric anhydrides have in many cases proved to be suitable substrates for enantioselective ester hydrolysis or anhydride opening, respectively, by means of organocatalysts,[9] transition metal complexes,[10] and hydrolytically active enzymes.[11] Hence, starting from structurally simple and easily accessible prochiral 3-benzyloxyglutarates we aimed for the development of a novel reaction cascade that would directly combine an optical activity generating desymmetrization with a complexity-creating oxonium ylide rearrangement and thus yield synthetically valuable, highly functionalized tetrahydrofuranones in a very concise fashion (Scheme 2).

Scheme 2. Proposed Desymmetrization/Rearrangement Sequence towards Functionalized Tetrahydrofuranones



For the preparation of the desired prochiral benzyl ethers initial studies revealed that reductive etherification employing diethyl 3-hydroxyglutarate and substituted benzaldehydes based on a slightly modified protocol of Nishizawa's method was most suitable and convenient.[12] We chose benzyl ether **4a** as a model for the development of a biocatalytic desymmetrization procedure. A series of hydrolases with precedence in the enantioselective glutarate hydrolysis were tested at static pH with regard to their ability to generate optically enriched monoester **5a**. Among those enzymes, lipase from *Candida antarctica* type B distinguished itself as a highly selective catalyst for the desired reaction, particularly when an aqueous protein preparation was employed instead of the more commonly used polyacrylate supported enzyme. Thus, (*S*)-**5a** was obtained in 93% yield and greater 99% *ee* (Scheme 3). Gratifyingly, the serine-protease α-chymotrypsin showed activity in the hydrolysis of **4a** too, however, giving rise to the (*R*)-configured product in good yield and 84% enantiomeric excess. Hence, simply by the right choice of the biocatalyst either enantiomer of the desired monoester can be obtained in good to excellent optical purity. From enantiopure (*S*)-**5a**, various protocols for the conversion into diazo ketone **7a** were subsequently examined. Unfortunately, classical carboxylate activation via its acid chloride or mixed anhydride followed by treatment with diazomethane turned out rather unsuccessful, mainly suffering from formation of the corresponding α-chloroketone. Chloride-free activating agents such as EDC or Boc_2O on the other hand were inefficient.[13] In order to avoid the undesired reaction of **7a** with hydrogen chloride or its ammonium salts, Alcántara and de Kimpe's procedure employing CaO as a scavenger was tested and proved to be the method of choice for the diazo ketone synthesis,[14] allowing for the preparation of **7a** in 88% isolated yield.

Scheme 3. Enzyme-Mediated Enantioselective Hydrolysis of **4a**



With diazo ketone **7a** in hand, we started our studies on the second key transformation of the planned reaction sequence. Thus, **7a** was treated with a series of metal complexes (Rh: 1 mol %, Cu: 5 mol %) to test their potential as a catalyst for the oxonium ylide rearrangement giving *C*-benzylated tetrahydrofuranone **6a**. Not surprisingly, in particular, complexes based on copper and rhodium showed the most promising behavior.[15] One class of benchmark catalysts for various diazo-activating transformations, the copper(II) acetylacetonates, failed to qualify as catalysts for the desired reaction, due to either the lack of activity or low product selectivity (Table 1, entries 1 and 2). On the other hand, employing copper(I) complexes, the rearrangement product **6a** was detected as the major product with moderate conversion and diastereoselectivity (Table 1, entry 3). Switching to rhodium-based systems, a

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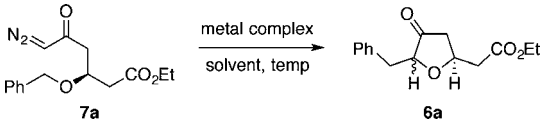
(15) Various gold and ruthenium complexes known for oxonium ylide chemistry failed to yield tetrahydrofuranone **6a**.

strong influence of the carboxylate ligand was observed. While rhodium trifluoroacetate did not lead to the formation of **6a**, the triphenylacetate complex gave rise to the tetrahydrofuranone in high yield, though, with rather modest *trans*-selectivity (Table 1, entries 4 and 5). Substantial improvement in the diastereoselectivity was observed employing the rhodium octanoate and acetate complexes, respectively (Table 1, entries 6 and 7).[16] Both rhodium dimers allowed for the rearrangement at low temperature (0 °C) reaching complete conversion within less than 1 h.[17] Dichloromethane turned out to be the optimal solvent for this transformation. The use of dichloroethane or benzene resulted in a slightly decreased yield of **6a** (Table 1, entries 8 and 9) while other solvents such as THF or toluene led to a pronounced formation of side products.

To evaluate for scope and limitations of the developed reaction sequence, a set of six benzylic ethers was tested with regard to the influence of substituents on enantio- and diastereoselectivity. To our delight, independently of the nature of the benzylic group, excellent optical purities were obtained in the CALB-mediated desymmetrization. Together with generally high yields of the monoesters **5**, the biocatalytic hydrolysis protocol proved to be an excellent tool for the multigram scale preparation of enantiopure benzyloxyglutarates (Scheme 4). Next, the activation–rearrangement sequence was studied. In order to avoid isolation of the intermediate diazo ketones, a two-step/one-purification route was pursued. As opposed to the enzymatic desymmetrization, the oxonium ylide rearrangement showed very distinct differences in selectivity depending on the character of the substituents at the benzylic moiety. While high *trans*-selectivity and good overall yield were obtained in the synthesis of **6a**, the naphthyl- and anisyl-substituted products **6b** and **6c** exhibited a significantly lower preference for the *trans*-isomer. Even more pronounced, rearrangement of the piperonyl derivative **5d** gave rise to tetrahydrofuranone **6d** with modest selectivity favoring the *cis*-product. On the other hand, electron-withdrawing groups such as nitro- or bromo-substituents helped to improve the preference for the *trans*-configured products. While rearrangement of the *p*-nitrobenzyl ether **5e** still suffered from low product selectivity (15% yield of **6e**), the reaction cascade starting from the symmetric bromo-substituted ether **4f** not only combined very high enantio- and diastereoselectivities with good overall yield but also moreover gave access to a highly functionalized building block (**6f**) that would potentially allow for subsequent manipulations by means of various transition metal-catalyzed cross-coupling reactions. Although in-depth studies are certainly required to gain further insight into mechanistical aspects of this Stevens-type rearrangement, the obvious influence of the nature of the aryl substituents on diastereoselectivity strongly supports a previously proposed fragmentation/recombination pathway.[4a,18,19]

Despite the fact that useful diastereoselectivities were achieved in the oxonium ylide rearrangement, a major

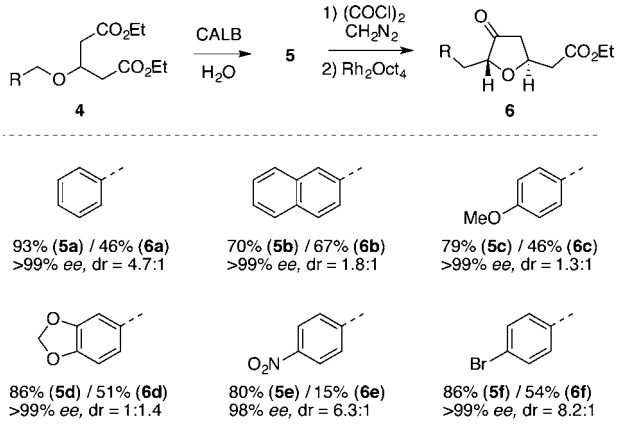
Table 1. Catalyst Screening for the Rearrangement of (*S*)-**7a**[a]



no.	metal complex	solvent	temp [°C]	time [h]	**6a** [%]	*trans*:*cis*
1	$Cu(acac)_2$	DCM	40	24	no reaction	
2	$Cu(hfacac)_2$	DCM	40	24	complex mixture	
3	$[Cu(MeCN)_4]PF_6$	DCM	rt	24	50	2.9:1
4	$Rh_2(O_2CCF_3)_4$	DCM	rt	24	no reaction	
5	$Rh_2(O_2CCPh_3)_4$	DCM	rt	5	81	1.9:1
6	$Rh_2(O_2CC_7H_{15})_4$	DCM	0	0.5	79	4.4:1
7	$Rh_2(O_2CCH_3)_4$	DCM	0	1	80	4.0:1
8	$Rh_2(O_2CCH_3)_4$	DCE	0	1	69	4.5:1
9	$Rh_2(O_2CCH_3)_4$	benzene	0	1	68	3.5:1

[a] Reaction conditions: **7a** (0.5 mmol), Cu- (25 μmol) or Rh-complex (5 μmol) in 10 mL of anhydr. solvent. Yield and diastereomeric ratios were determined by ^{1}H NMR using anisol as an internal standard.

Scheme 4. Influence of Substituents in the Desymmetrization–Rearrangement Cascade[a]



[a] Optical purity determined by chiral HPLC after derivatization with (*S*)-1-phenylethylamine. Diastereomeric ratios determined by ^{1}H NMR from the crude reaction mixture. For **5**: isolated yield on 3.5 mmol scale; for **6**: isolated yield on 1 mmol scale over two steps (from **5** to **6**) without purification of intermediate diazoketones.

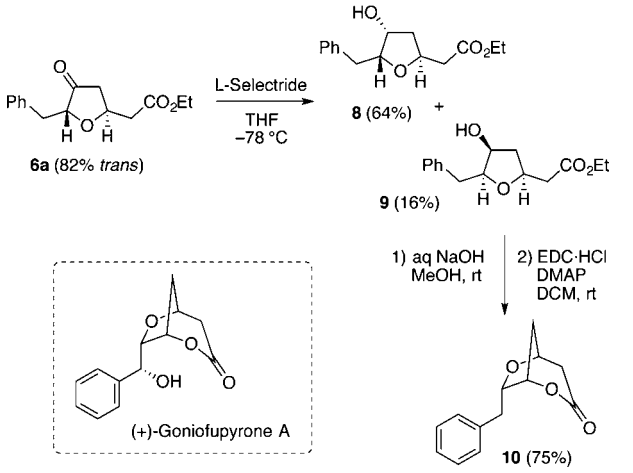
(16) The *trans*-relationship of the major isomer was assigned by NOE experiments.

(17) Complete conservation of enantiopurity was confirmed by HPLC.

(18) Recent examples: (a) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657–1660. (b) Murphy, G. K.; West, F. G. *Org. Lett.* **2005**, *7*, 1801–1804. (c) Sharma, A.; Guénée, L.; Naubron, J.-V.; Lacour, J. *Angew. Chem.* **2011**, *123*, 3761–3764. *Angew. Chem., Int. Ed.* **2011**, *50*, 3677–3680. (d) Jaber, D. M.; Burgin, R. N.; Helper, M.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2012**, *14*, 1676–1679.

(19) Preliminary studies on [2,3]-sigmatropic glutarate rearrangements reveal the selective formation (dr > 20:1) of *trans*-diastereomers. We thus assume that high selectivity in the initial formation of *trans*-oxonium ylides is depleted more or less severely during the [1,2]-sigmatropic rearrangement.

Scheme 5. Application in the Synthesis of 7-Deoxygoniofupyrone A



requirement for its synthetic applicability—the separation of the *trans*-products from the minor isomer—appeared to be a nontrivial task for all tetrahydrofuranones. However after simple reduction of the resulting *cis*/*trans*-mixtures by means of L-selectride, two epimeric alcohols (**8** and **9**) (Scheme 5) were obtained that could be easily separated by flash chromatography. As illustrated with the preparation of 7-deoxygoniofupyrone A (**10**)[20] by simple lactonization of **9**, these tetrahydrofurans represent valuable building blocks with bright prospects to find application in the synthesis of complex target structures.

In summary, a concise and selective synthetic protocol toward highly functionalized tetrahydrofurans was established. Modern transition metal catalysis in concert with enantioselective biocatalysis provides a very straightforward route to access valuable chiral building blocks from simple symmetric glutarates. The extension of this strategy toward substrates allowing for [2,3]-sigmatropic rearrangements as well as applications in natural product synthesis are currently ongoing tasks in our laboratory.

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Supporting Information Available. Full analytical data and copies of ^{1}H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Lan, Y.-H.; Chang, F.-R.; Liaw, C.-C.; Wu, C.-C.; Chiang, M.-Y.; Wu, Y.-C. *Planta Med.* **2005**, *71*, 153–159.

The authors declare no competing financial interest.