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Oxidation of Substituted Cyclopentane-1,2-diones

KAROLIN OJA

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TALLINN UNIVERSITY OF TECHNOLOGY
School of Science
Department of Chemistry and Biotechnology
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Supervisor: Professor Margus Lopp
School of Science
Tallinn University of Technology
Tallinn, Estonia

Co-supervisor: Senior Researcher Anne Paju
School of Science
Tallinn University of Technology
Tallinn, Estonia

Opponents: Prof Eugenijus Butkus
Faculty of Chemistry
Vilnius University

Assoc. Prof Uno Mäeorg
Department of Chemistry
University of Tartu

Defence of the thesis: May 16th, 2018, Tallinn

Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for doctoral or equivalent academic degree.

Karolin Oja

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Asendatud tsüklopentaan-1,2-dioonide oksüdeerimine

KAROLIN OJA

TTÜ KIRJASTUS

Contents

List of Publications

The list of author's publications, on the basis of which the thesis has been prepared:

I Paju, A.; Oja, K.; Matkevitš, K.; Lumi, P.; Järving, I.; Pehk, T.; Lopp, M. Asymmetric synthesis of tertiary 2-substituted 5-oxotetrahydrofuran-2-carboxylic acids. *Heterocycles* **2014**, *88*, 981-995.

II Maljutenko, K.; Paju, A.; Järving, I.; Pehk, T.; Lopp, M. Kinetic resolution of epoxy alcohols with the Sharpless Ti-isopropoxide/tartaric ester complex. *Tetrahedron: Asymmetry* **2016**, *27*, 608−613.

III Maljutenko, K.; Borovkov, V.; Kananovich, D.; Järving, I.; Lopp, M. Aerobic cascade oxidation of substituted cyclopentane-1,2-diones using metalloporphyrin catalysts. *Tetrahedron* **2018**, *74*, 661-664.

Author's Contribution to the Publications

Contribution to the papers in this thesis are:

I Planning and carrying out part of the experiments, characterization of some obtained products, minor role in the manuscripts preparation.

II Planning and carrying out all of the experiments, characterization of the obtained products, major role in the manuscripts preparation.

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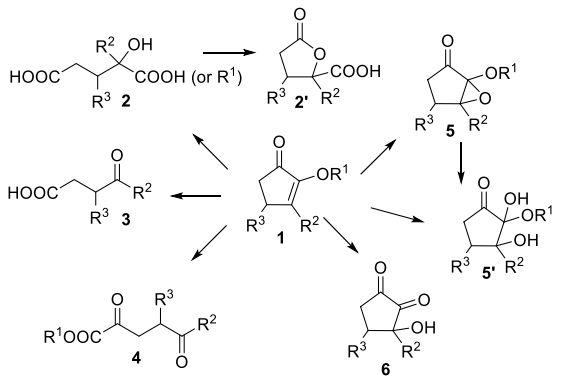
Introduction

In organic synthesis, there is an enormous toolbox of methods for different chemical transformations, although the tools are not universal and in many cases a new type of substrate demands a specific chemical instrument. This creates the need for the constant development of new procedures in order to overcome substrate-caused limitations. Nowadays, efficiency, safety and environmental feasibility are the key words in the development of new procedures for chemical syntheses. These are the driving forces behind discovering new and improving previously known methods, modifying them and in many cases, applying nature-inspired catalysts to achieve better stereo-, chemo- and enantioselectivities.

Oxidation is one of the fundamental reactions in organic chemistry, as well as in living organisms. In the year 2016, nearly 50,000 articles on oxidation reactions were published according to Web of Science, and there has been a steady increase in them over the recent years.

Substituted cyclopentane-1,2-diones are reactive organic molecules which undergo many chemical reactions. The reaction pathway usually depends on the reagent and the substrate structure: the nature of the substituent, keto-enol equilibrium *etc*. In oxidation reactions, these compounds may be oxidized in different ways and to different extents. Substituted cyclopentane-1,2-diones can also be epoxidized, hydroxylated and oxidatively cleaved in different ways (*via* a Baeyer-Villiger reaction, 1,2-diol cleavage *etc*.), yielding a variety of products: keto-epoxides, 3-hydroxylated 1,2-diketones, dicarboxylic acids, lactone carboxylic acids, ketoacids and diketoacids (Scheme 1). Since the products of these oxidation reactions are useful intermediates for the synthesis of many compounds, the development of chemo- and stereoselective methods of oxidation is of great value and importance.



Scheme 1. *Oxidation products of substituted cyclopentane-1,2-diones.*

The present thesis summarizes the recent progress made by us in the oxidation of substituted cyclopentane-1,2-diones.

The Sharpless catalyst has been used for the asymmetric oxidation of cyclopentane-1,2-diones for around two decades now. In the present work, a general method has been described by using a non-stoichiometric amount of the catalyst for the synthesis of different dicarboxylic acids (transforming to lactone carboxylic acids) with high

enantioselectivity, which completes this series of studies on the synthesis of enantiomeric lactone carboxylic acids. We also made an attempt to obtain enantiomeric ketoepoxides: valuable multifunctional intermediates for chemical synthesis. Furthermore, we studied the properties of epoxides of substituted cyclopentane-1,2-diones under kinetic resolution conditions and developed a method for the synthesis of enantiomerically enriched epoxides, as well as cyclic dihydroxy acetals.

Possibilities of using organocatalysts for the oxidation of substituted cyclopentane-1,2-diones were also studied. However, it was found that the reaction is not efficient: different types of products in small amounts were formed. The thesis also covers the oxidative cleavage of substituted cyclopentane-1,2-diones with metalloporphyrins, including using molecular oxygen from air as an oxidant, resulting in the ring cleavage products dicarboxylic acids, ketoacids and diketoacids (Scheme 1).

Abbreviations (optional)

Ac	acetyl
AcOH	acetic acid
BINOL	1,1'-Bi-1-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bz	benzoyl
BTSP	bis(trimethylsiloxy)phosphine
Cy	cyclohexyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
ee	enantiomeric excess
GLC	gas-liquid chromatography
HF x Py	hydrogen fluoride pyridine complex
*i*Pr	isopropyl
mCPBA	*meta*-chloroperbenzoic acid
MOF	metal-organic framework
MOM	methoxymethoxy
MP	metalloporphyrin
NADH	nicotinamide adenine dinucleotide
NMR	nuclear magnetic resonance
OEP	octaethylporphyrin
Ph	phenyl
PhI	iodobenzene
PhIO	iodosobenzene
PTC	phase transfer catalyst
SAE	Sharpless asymmetric epoxidation
*t*Am	*tert*-amyl
TBAF	tetra-*n*-butylammoniumfluoride
TBS	*tert*-butyldimethylsilyl
*t*BuOH	*tert*-butanol
*t*BuOOH	*tert*-butylhydroperoxide
THF	tetrahydrofuran
TPFPP	tetra(pentafluoro)phenylporphyrin
TPP	tetraphenylporphyrin

1 Literature overview

The overview covers the oxidation methods of different compounds, focusing on the oxidation systems used in this work. In addition, the uses and reactions of epoxides and lactone acids are discussed, providing insight into their practical value.

1.1 Oxidation methods

Oxidation reactions are generally considered to be the addition of an atom more electronegative than carbon, or the loss of a hydrogen atom from a molecule. In this overview, we use the term oxidation only to refer to the addition of an oxygen atom to a molecule. Some widely used oxidation reactions are the dihydroxylation, epoxidation and oxidative cleavage of alkenes, the oxidation of alcohols to aldehydes and carboxylic acids, and amines to amides and nitriles, and the oxidation of many other functional groups, such as β-lactams, phenols, hydrocarbons, carbonyl compounds and sulfides.[1]

Of the enormous number of methods in the literature, we focus on the methods of oxidation of the double bond, mainly epoxidation, the oxidative cleavage of double bonds and the Baeyer-Villiger oxidation at a carbonyl group. The interest in the development of efficient, sustainable and environmentally friendly processes is increasing, and this is also the case with oxidation reactions.

1.1.1 Epoxidation

Epoxidation is a widely used chemical procedure in laboratory and industrial processes. Epoxidation reactions can be performed with direct peroxide oxidation, by using transition-metal catalysis, by using organocatalysts, with manganese catalysts *etc*. All of these methods have different environmental impacts that must be considered by chemists. Even simpler oxidation processes, such as the production of propylene oxide (one of the more important starting compounds in the chemical industry), which is commonly based on chlorohydrin,[2] have several disadvantages, including the formation of chlorinated 1,2-dichloropropane and dichloroisopropyl ethers as by-products. For this reason no new chlorohydrin plants are being built.[3] In the competing hydroperoxide process,[4] the alkane is peroxidized to an alkyl-hydroperoxide that reacts with propene, producing propene oxide and an alcohol. Compared with the chlorohydrin process, it is more selective and produces less waste. However, the method produces unwanted co-products, and yet more efficient epoxidation methods are needed.

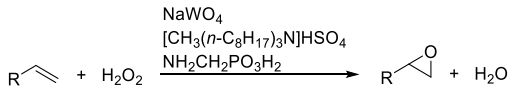
In transition metal catalysis for epoxidation, there are several terminal oxidants available, such as hydroperoxides, hypochlorite and iodosylbenzene, which are unfortunately not efficient in terms of active oxygen content. However, they usually offer better product selectivity than the environmentally and ecologically preferable oxidation reactant: molecular oxygen (Table 1).[1]

Table 1. Oxidants used in transition metal-catalysed epoxidations, and their active oxygen content.

Oxidant	*Active oxygen content (wt.%)*	*Waste product*
Oxygen (O_2)	100	Nothing or H_2O
Oxygen (O_2)/reductor	50	H_2O
H_2O_2	47	H_2O
NaOCl	21.6	NaCl
CH_3CO_3H	21.1	CH_3CO_2H
*t*BuOOH (TBHP)	17.8	*t*BuOH
$KHSO_5$	10.5	$KHSO_4$
BTSP	9	hexamethyldisiloxane
PhIO	7.3	PhI

The catalytic processes are more reactive and selective compared to hydrogen peroxide. With transition metals, such as titanium, vanadium, molybdenum and tungsten, *tert*-butyl hydroperoxide is often used as the terminal oxidant, as in the case of Sharpless asymmetric epoxidation.[5] Hydrogen peroxide, however, can give better results in cases of heterogeneous titanium(IV)-silicate catalysts (TS-1), where the substrates are adsorbed in the micropores of the catalyst, thus preventing the inhibition of oxidation by water.[6] In the field of homogeneous catalysis, sodium tungstate, (aminomethyl)phosphonic acid and methyltri-*n*-octylammonium bisulfate in 2:1:1 ratio have been found to catalyse the epoxidation of different alkenes with hydrogen peroxide as a terminal oxidant, without the use of chlorinated solvents (Table 2).[7]

Table 2. Tungsten-catalysed epoxidation with hydrogen peroxide.

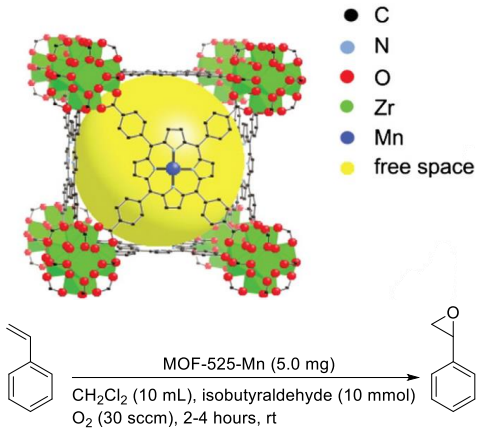


No.	*Alkene*	*Time (h)*	*Conversion (%)*	*Yield (%)*
1	1-octene	2	89	86
2	1-decene	2	94	93
3*	1-decene	4	99	99
4*	allyl octyl ether	2	81	64
5*	styrene	3	70	2

*20 mmol alkene in 4 mL toluene

Even though the selectivities of the often used terminal oxidants are better than that of molecular air oxygen, epoxidation reactions are also performed with O_2, for example by using manganese catalysts.[8] Of the catalytic systems, manganese-based systems are among the most developed. For example, a chiral manganese porphyrin-based metal-organic framework complex has been proposed as a catalyst for the epoxidation of alkenes with molecular oxygen (Scheme 2).[9] The oxidation mechanism involves the incorporation of one oxygen atom of the oxygen molecule into the epoxide while the other is transferred to the added co-reductant.[10] The main drawback of that system is

the narrow scope of suitable substrates and the fact that the epoxidation of (*Z*)-olefins leads to significant amounts of *trans*-epoxide as a byproduct.[8]



***Scheme 2**. Epoxidation of styrene using MOF-525-Mn and molecular oxygen.*

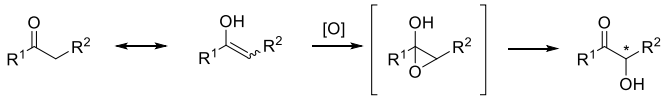
As iron is the most common metal on earth and it acts as an oxygen carrier in biological systems, cheap and environmentally friendly iron-containing systems are also used for oxidation. For example, Simonneaux *et al.* used a chiral iron porphyrin for the epoxidation of substituted styrenes with the products obtained in 8-70% *ee*.[11] The drawback common with most Fe and Mn systems that use H_2O_2 as the oxidant is the decomposition of the hydrogen peroxide, which leads to its overconsumption.[8]

Ruthenium-containing systems have been developed by Che *et al*., using a chiral ruthenium porphyrin for the epoxidation of conjugated olefins with molecular oxygen without reductant, achieving *ee* values up to 73%.[12] However, these catalyst systems are rather underdeveloped because of their high catalyst loading (5 mol%), limited substrate scope and low enantioselectivities compared to Mn- and Fe-based systems.

1.1.2 Oxidation of carbonyl compounds

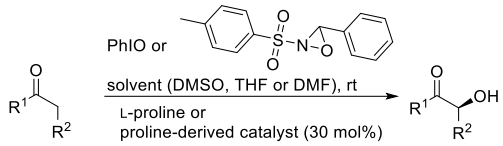
Carbonyl compounds, such as aldehydes (alkanals) and ketones (alkanones), can be oxidized with different methods to obtain carboxylic acids and their derivatives.[1] For aldehydes, the oxidants can be metal-free, such as oxygen[13] and peroxides,[14] or metal-based, such as manganese,[15] chromium,[16] copper[17] and silver,[18] or several halogen-based oxidants.[19]

Keto-enol tautomerism creates a C=C bond which can undergo epoxidation. The oxidation of ketones predominantly occurs through the oxidation of its enol or enolate form. This can result in α-hydroxy ketones through the rearrangement of unstable epoxide intermediates (Scheme 3).[20] This feature has been used by chemists to create synthetically valuable compounds.



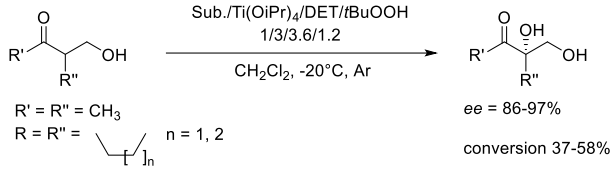
***Scheme 3.** Epoxidation of an enol.[20]*

For example, proline catalysts and PhIO or *trans*-2-(p-methylphenylsulfonyl)-3-phenyloxaziridine as an oxidant have been used to synthesize various α-hydroxy ketones through an enamine form, with up to 77% *ee* (Scheme 4).[21]



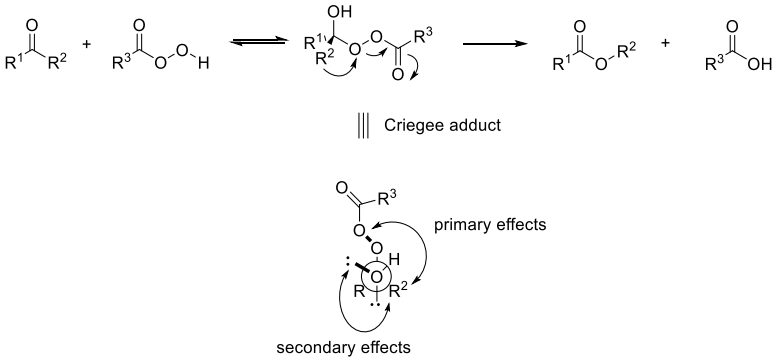
Scheme 4. *Direct organocatalytic asymmetric α-oxidations of ketones.*

Using the Sharpless complex, our group has shown that optically active hydroxylated products can be obtained with high *ee* values (up to 97%) and with reasonable conversions (up to 58%) under epoxidation conditions (Scheme 5).[22,23]



Scheme 5*. Asymmetric α-hydroxylation of ketones.*

The Baeyer-Villiger oxidation[24] is one of the most well-known reactions in organic synthesis and a variety of carbonyl compounds can be oxidized using this method: ketones to esters, cyclic ketones to lactones, benzaldehydes to phenols and carboxylic acids to anhydrides.[25] The carbon-carbon bond cleavage at the carbonyl group can result in carboxylic acids by Baeyer-Villiger oxidative rearrangements of ketones. When the ketone is asymmetrical, the migrating group in the cleavage using Baeyer-Villiger oxidation depends on the migratory aptitude, and is generally the more electron-releasing and substituted one.[26,27] This feature of the reaction has been widely used in organic synthesis (Scheme 6).



Scheme 6*. Baeyer-Villiger oxidation.*

The Baeyer-Villiger oxidation employing metal catalysts has been conducted with hydrogen peroxide and platinum complexes (Figure 1, **I**),[28] palladium complexes (Figure 1, **II**),[29] cobalt-salen complexes (Figure 1, **III**) [30] and second-generation zirconium-salen complexes (Figure 1, **IV**).[31] Examples of metal-free systems for Baeyer-Villiger oxidation include those using chiral bisflavanium perchlorates (Figure 1, **V**),[32] BINOL-derived phosphoric acids (Figure 1, **VI**) [33] and oligopeptide catalysts (Figure 1, **VII**).[34]

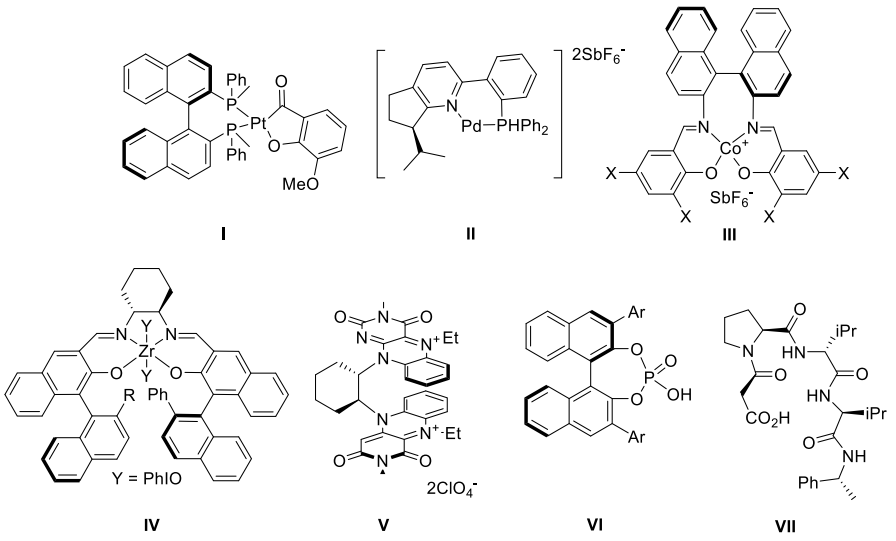
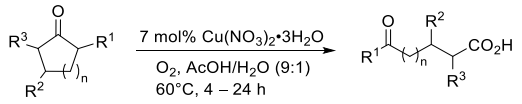


Figure 1. *Metal-based and metal-free catalysts for asymmetric Baeyer-Villiger oxidation.*

Simple acyclic ketones can be oxidized and cleaved using a haloform reaction, as well as cyclic ketones and functionalized ketones with substituents in the α-position. Together with carboxylic acids, dicarbonyl compounds are formed.[1]

For the oxidation of ketones, other catalysts, such as copper salts, can also be used to create oxidative cleavage of the substrate (Scheme 7).[17]



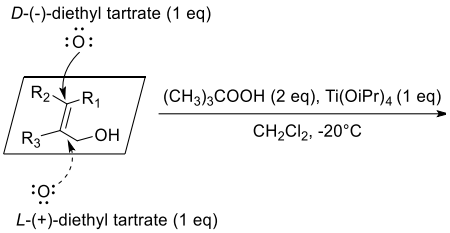
Scheme 7. *Oxidative cleavage of cycloalkanones with copper and oxygen.*[35]

1.1.3 Sharpless catalyst

Barry Sharpless was awarded the Nobel prize in 2001 for his major contributions in the field of asymmetric epoxidation, which has been recognized as one of the most important achievements of synthetic chemistry in the last decades. The discovery involves a metal-catalysed asymmetric epoxidation process, using (+)- or (–)-diethyl tartrate, titanium tetraisopropoxide to build a catalytic complex with the substrate and

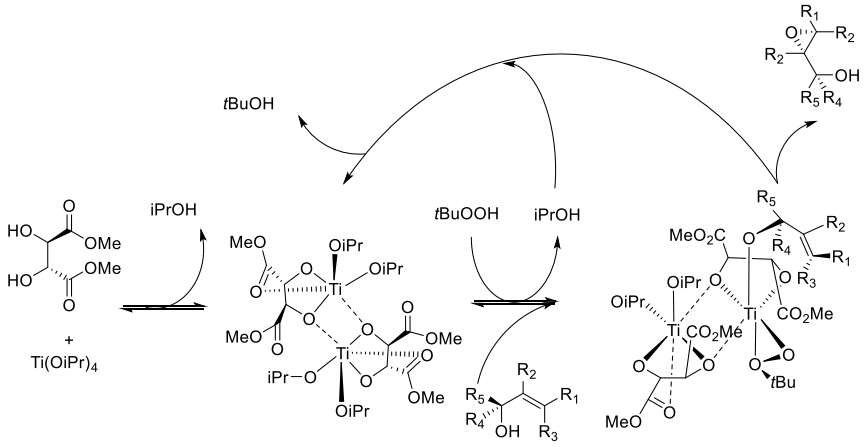
*t*BuOOH, affording a high level of asymmetric induction for the allylic alcohol (Scheme 8).[5]

In Scheme 8 it can be seen that in the catalytic system the olefinic unit is placed on a plane with the hydroxymethyl moiety at the bottom right, (+)-DET as an asymmetric inducer leads to oxygen addition from the bottom while the use of (–)-DET leads to oxygen addition from the top.[5] The enantioselectivity of this reaction mainly depends on the different substituents at the substrate (allylic alcohol), while titanium tetraisopropoxide as the source of the titanium species and *tert*-butylhydroperoxide as an oxidant are the reagents of choice to obtain epoxy alcohols. It must be taken into consideration that epoxy alcohols are sensitive to a ring-opening process,[36] a property which can be used for the kinetic resolution of ketones.



Scheme 8. *Sharpless epoxidation oxygen addition.*

The catalyst for Sharpless epoxidation is a bimetallic Ti-complex that binds together two tartaric esters (asymmetric inducer), hydroperoxide (reagent) and allylic alcohol (substrate) (Scheme 9). In the catalytic species, the hydroperoxide occupies the equatorial site and one of the axial sites (the lower one because of sterical demands), and the allylic alcohol is in the remaining axial site.



Scheme 9. *Sharpless epoxidation mechanism.*

To transfer the oxygen atom, the distal oxygen is placed in the equatorial position. In the epoxidation process, the dihedral angle for the allylic moiety is very small (O-C-C=C,

ca. 30°), which explains the lower enantioselectivity for *Z*-substituted substrates (Scheme 9).[36,37]

The Sharpless complex can be used both for the enantioselective epoxidation of prochiral primary allylic alcohols and for the kinetic resolution of racemic secondary allylic alcohols.[38] The enantioselectivity of the Sharpless epoxidation reaction of secondary allylic alcohols comes from the kinetic resolution reaction, where one of the enantiomers reacts much faster than the other. This dependence from relative rate can be seen in Figure 2.

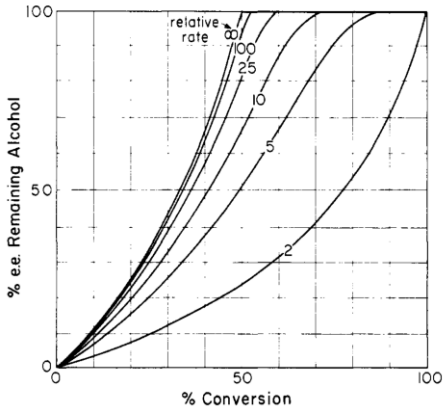
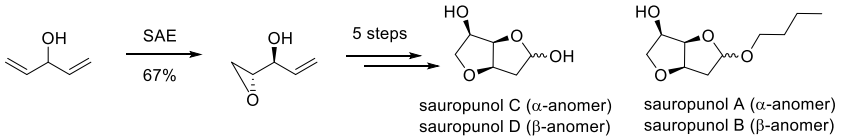
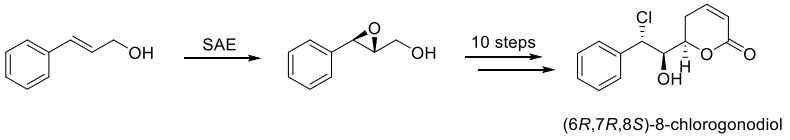


Figure 2. *Dependence of enantiomeric excess on relative rate.*[38]

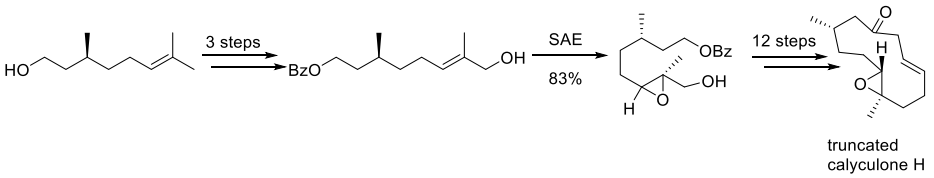
The finding of Sharpless has largely expanded the scope of asymmetric synthesis to produce antibiotics, anti-inflammatory drugs and the like.[39] Even recently, the Sharpless asymmetric epoxidation has been used as a key synthetic step in the synthesis of many biologically active compounds, including sauropunols A-D (antibacterial, anti-inflammatory and analgesic compounds,[40] Scheme 10), (6*R*,7*R*,8*S*)-8-chlorogonodiol (anti-inflammatory properties, scheme 11),[41] and a truncated calyculone H analogue (containing the basic ring system, which may be the key pharmacophore to interact with cellular targets for anticancer properties, Scheme 12).[42]



Scheme 10. *Synthesis of sauropunols A-D.*



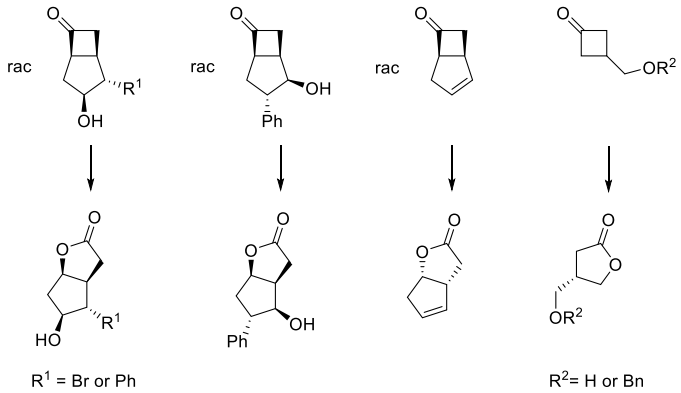
Scheme 11. *Synthesis of (6R,7R,8S)-8-chlorogonodiol.*



Scheme 12. *Synthesis of truncated calyculone H*.

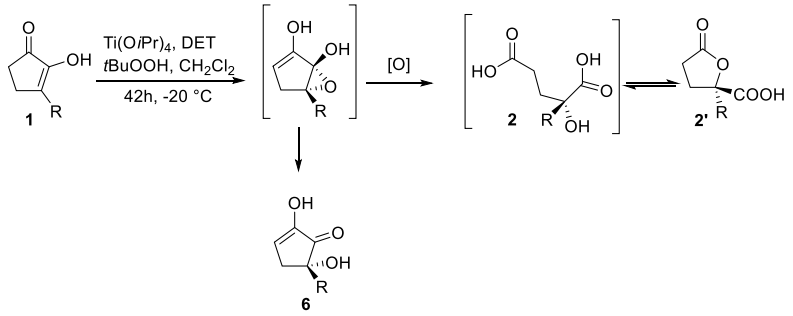
1.1.4 Use of Sharpless catalyst for the oxidation of ketones

While the Sharpless catalyst has mostly been used for the oxidation of allylic alcohols, yielding enantiomerically enriched epoxyalcohols as products, there are also other uses for the complex, e.g. the asymmetric oxidation of sulphur.[43] By using a modified procedure, the use of the Ti/TADDOL/*t*BuOOH complex in the oxidation of cyclobutanones to lactones *via* Baeyer-Villiger oxidation has been studied in our group (Scheme 13).[44]



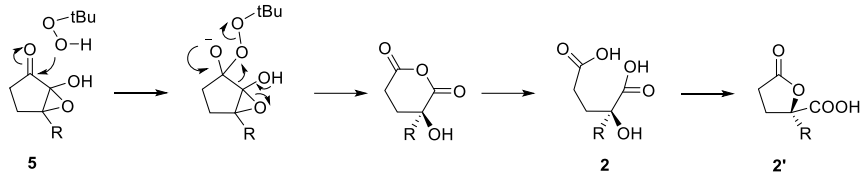
Scheme 13. *Baeyer-Villiger oxidation using a modified Sharpless catalyst.*

It has been shown that the Sharpless complex can also be applied for the oxidation of cyclopentane-1,2-diones.[45] The reaction proceeds via a cascade that first includes epoxidation (resulting in an α-hydroxylation product), followed by Baeyer-Villiger oxidation and acylation. In all cases, the epoxide is an intermediate.[46, 47,48] As a result, lactone carboxylic acids are formed as the main products (Scheme 14).



Scheme 14. *Oxidation of 3-alkyl cyclopentane-1,2-diones under Sharpless oxidation conditions.*

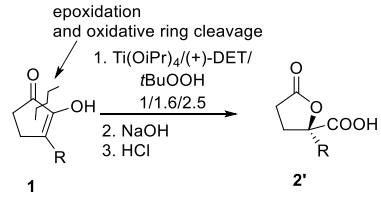
When investigating the mechanism of oxidation, it was found that after the initial epoxidation step, Baeyer-Villiger oxidation occurs, resulting in diacids **2** and lactone carboxylic acids **2'**.[49] For example, under Sharpless conditions epoxidation has been considered the possible rate-limiting step in the oxidation of these cyclic compounds and the Baeyer-Villiger oxidation has subsequently proceeded, cleaving the cycle. Scheme 15 represents the whole process.



Scheme 15. *Baeyer-Villiger oxidation after the forming of epoxide* ***5****.*[49]

The results using the Sharpless catalyst in the oxidation of 1,2-cyclic diketones are presented in Table 3 where it can be seen that using the method, it is possible to obtain enantiomeric 2-alkyl-2-hydroxyglutaric acid γ-lactones and DAG-lactone templates.

Table 3. Asymmetric oxidation of 3-alkyl-1,2-cyclopentanedione with Sharpless catalyst.[50]



R = a) $-CH_3$; b) $-C_2H_5$; c) $-CH_2$-OBn;
d) $-CH_2CH_2$-OMOM; e) $-CH_2CH_2$-OBn; f) -Bn

			Isolated lactone acid 2'	
No.	***Substrate***	***R***	***Yield (%)***	***ee (%)***
1	**1a**	$-CH_3$	75	93
2	**1b**	$-C_2H_5$	72	93
3	**1c**	$-CH_2$-OBn	75	96
4	**1d**	CH_2CH_2-OMOM	69	94
5	**1e**	$-CH_2CH_2$-OBn	71	95
6	**1f**	-Bn	83	96

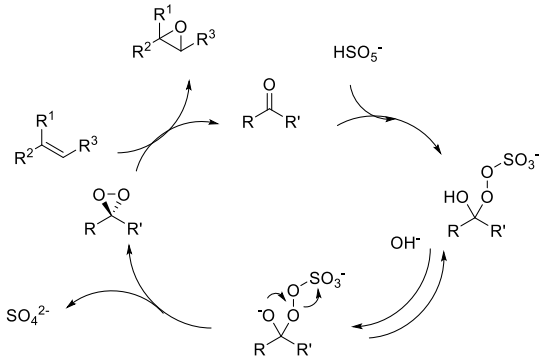
Furthermore, while a great deal of progress has also been made in the field of the oxidation of cyclic 1,2-diketones, using the Sharpless catalyst in stoichiometric amounts has so far remained a problem: the best results have been obtained with a $Ti(OiPr)_4$/DET/*t*BuOOH ratio of 1/1.6/2.5 and the ratio of $Ti(OiPr)_4$ to the substrate 1:1.

To conclude, the oxygenation reactions mentioned in 1.1.1-1.1.4 have room for improvement in the field of selective reactions using environmentally benign oxidants and solvents. The most extensively used complexes for asymmetric oxygenation catalysis are ones involving transition metals, and organocatalysts are less used because of their low activities and efficiencies. However, they might be complementary

to metal catalysts.[8] Also, the revealed unique properties of the Ti/DET complex for the 3-alkyl cyclopentane-1,2-diones revealed the need to explore further opportunities for asymmetric synthesis. The opportunities to selectively obtain epoxides and other primary oxidation products are of the greatest interest.

1.1.5 Organocatalysis for oxidation reactions

Organocatalysis has emerged as a great alternative for metal-catalysed enantioselective oxidation reactions. For epoxidation, different organocatalytic approaches have been developed. One of the possibilities is the use of a ketone catalyst (Scheme 16), where, according to the mechanism, only a catalytic amount of ketone is needed, and the possibility of asymmetric epoxidation arises when chiral ketone catalysts are used. The development of a well-functioning system has, however, proved to be challenging.[51] The first reported asymmetric epoxidation of *trans*-β-methylstyrene and 1-methylcyclohexene was accomplished by Curci and co-workers, who used (+)-isopinocamphone (Figure 3, **VIII**) and (*S*)-(+)-3-phenylbutan-2-one (Figure 3, **IX**) as the ketone catalysts.[52] Replacing the simple ketones with those containing a trifluoromethyl group (Figure 3, **X** and **XI**) increased the rate of the epoxidation reaction.[53]



Scheme 16. *Ketone-catalyzed epoxidation of olefins.*

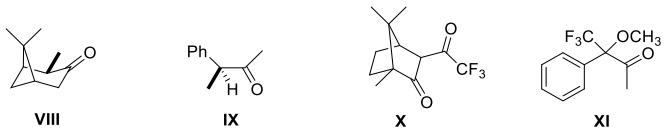
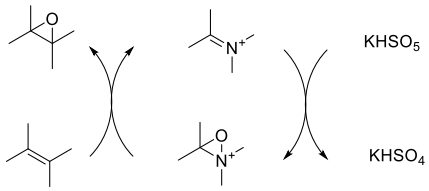


Figure 3. *Earlier ketone organocatalysts for epoxidation.*

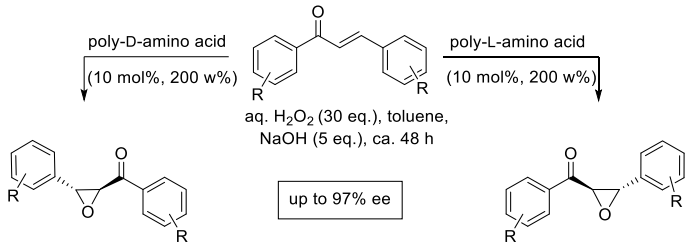
The ketones used for the epoxidation of olefins can be C_2-symmetric,[54] ammonium ketones,[55] bicyclo[3.2.1]octan-3-ones,[56] carbocyclic ketones[57] and ketones with an attached chiral moiety.[58] It is also possible to use chiral iminium salts,[59] where the iminium salt catalyst is regenerated upon epoxidation (Scheme 17).[51]



Scheme 17. *Catalytic cycle for iminium salt-catalyzed epoxidation.*

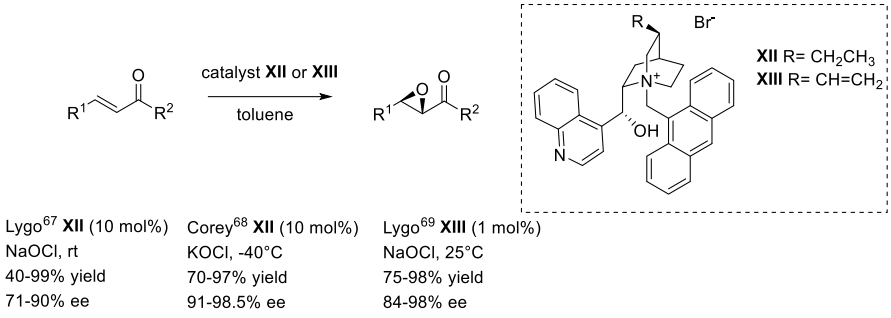
Oligopeptides are also attractive catalysts for asymmetric transformations, and were first proposed by the Juliá-Colonná method for epoxidation.[60] There are also phase-transfer catalysts,[61] secondary and primary amines[62] and cyclodextrins[63] used as catalysts.

In the synthesis of valuable ketoepoxides, polyamino acids are used as catalysts: the initial triphasic system (substrate in organic solvent treated with sodium hydroxide containing hydrogen peroxide and insoluble gel-like polyamino acid) can be replaced with a two-phase non-aqueous system, composed of a urea-hydrogen peroxide complex as an oxidant with a non-nucleophilic base or sodium percarbonate as a source of oxidant and base.[64] With three-phase systems, a phase-transfer co-catalyst or sodium percarbonate can be used as an oxidant/base and in this method, where the PLL catalyst is prepared in an improved manner, using high-temperature polymerisation of L-Leu-NCA, no pre-activation of the polyamino acid catalyst is necessary, the reaction time is decreased and, in some cases, the enantioselectivity is increased (Scheme 18).[65]



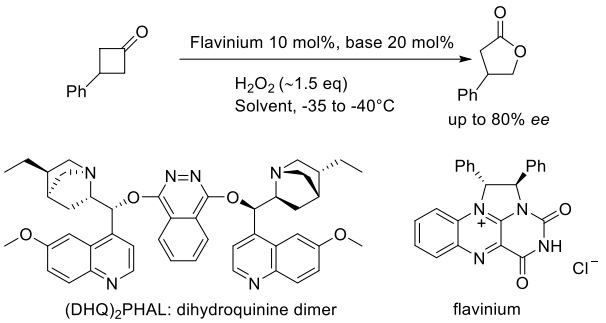
Scheme 18. *Epoxidation with polyamino acids.*

In asymmetric epoxidation reactions with phase transfer catalysts, the initial studies were made by Wynberg *et al.* in a biphasic Weitz-Scheffer epoxidation where α,β-epoxyketones were afforded with up to 54% *ee* values using chiral ammonium salts derived from cinchona alkaloids.[66] Further developments of the approach have been made by the groups of Lygo and Corey (Scheme 19). Lygo and co-workers demonstrated the use of PTC **XII,** where a 10 mol% loading in combination with NaOCl at room temperature afforded epoxides in yields up to 99% and enantioselectivities up to 90% with different substrates.[67] Corey's group demonstrated the possibility of using KOCl as an oxidant with the same catalyst in toluene at a lower temperature (-40°C).[68] Lygo's group also optimized the parameters for catalyst **XIII**, lowering the catalyst loading to 1 mol%.[69]



Scheme 19. *Epoxidation with PTC.*

It is also possible to get Baeyer-Villiger oxidation products by using organocatalysis. For example, 10-methylacridinium perchlorate has been used as an effective catalyst with hydrogen peroxide.[70] The problems with enantioselectivity have been solved by using chiral flavinium salts with a basic co-catalyst (cinchona alkaloid dimer) to obtain lactones with high stereoselectivity (Scheme 20).[71]



Scheme 20. *Baeyer-Villiger oxidation with organocatalysts.*

Significant advances have been made in the field of chiral organocatalysis to obtain valuable building blocks for the synthesis of biologically active compounds and pharmaceuticals. However, there is still room for improvement, especially for enantioselectivity, catalyst loading and substrate scope.

1.1.6 Metalloporphyrins for epoxidation and oxidative cleavage

Porphyrins and their derivatives are intense coloured macrocyclic compounds found in nature. They have been intensely investigated because of their role in life processes (*chlorophyll a* and *heme b* are metalloporphyrin derivatives; see Figure 4).

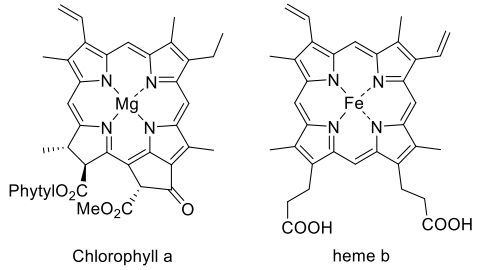
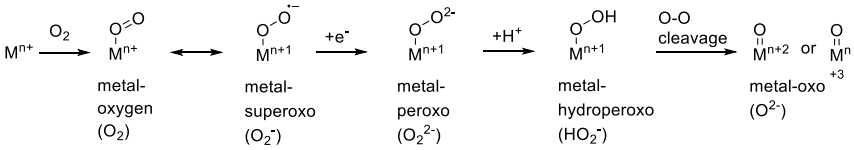


Figure 4. *Metalloporphyrin derivatives involved in life processes.*

Metalloporphyrins are well known as a prosthetic group of proteins and enzymes called hemoproteins.[72] Ever since the discovery of cytochrome P450, the use of metalloporphyrin catalysts has become an alternative for oxidation reactions[73] to substitute the stoichiometric use of such oxidizing agents as strong inorganic acids, peroxyacids or toxic oxo-metal oxidants.[74]

In oxidation reactions, they utilize common metal-oxygen intermediates in their mechanistic cycles. These are metal-superoxo ($O_2^{\bullet-}$), -peroxo (O_2^{2-}), -hydroperoxo (OOH^-) and -oxo (O^{2-}) (Scheme 21).[75]



Scheme 21. *Common metal-oxygen intermediates utilized by metalloproteins.*

Metalloporphyrins can be divided into three generations (Figure 5) based on their structures.[76] The first generation porphyrins have no substituents in the aryl moiety at the *meso* positions (such as Fe(TPP)Cl), the second generation porphyrins are *meso*-phenyl-substituted and have electronegative and bulky groups (such as *meso*-tetrakis(pentafluorophenyl)porphyrin iron(III) chloride), and the third generation porphyrins have electron-withdrawing groups (such as halogens) in the β-pyrrole positions of second generation porphyrins. The reason for the development of second and third generation porphyrins was to overcome the oxidative degradation of the first-generation porphyrin. The second-generation porphyrins are more resistant to degradation because of the hindered approach of the oxidants to the reactive *meso*-positions. The third-generation porphyrins have the added benefit of an increase in the electrophilicity of the metal-oxo active species.[77]

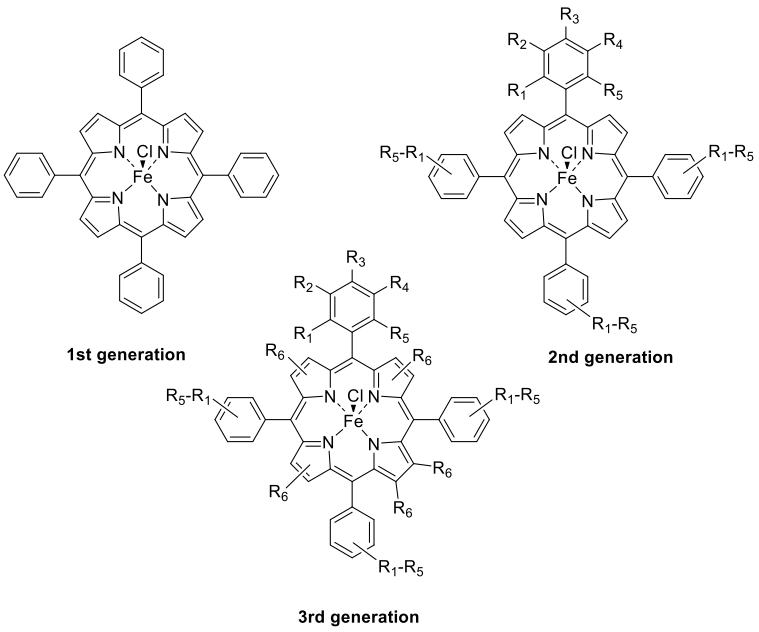
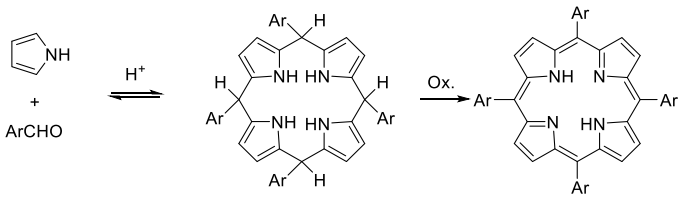


Figure 5. *Three generations of metalloporphyrins.*

The biggest challenge regarding the use of metalloporphyrins as catalysts is definitely the difficulty of their synthesis, which gives the macrocycle in 50% yields in the best cases, while normally ranging from about 10-20% (Scheme 22). The first reported synthesis of a porphyrin was accomplished by Rothemund in 1935,[78] but the two most used methods up to now are the Longo-Adler[79] and Lindsey[80] methods. The Longo-Alder method uses refluxing of aldehyde and pyrrole in propanoic acid to get the condensation product and, because it uses air for the oxidation of the porphyrinogen intermediate, it is not suitable for air-sensitive aldehydes. This problem can be overcome by using the Lindsey method, which is performed under argon and uses such oxidants as tetrachloro-1,4-benzoquinone (*p*-chloranil) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford the final porphyrin product.



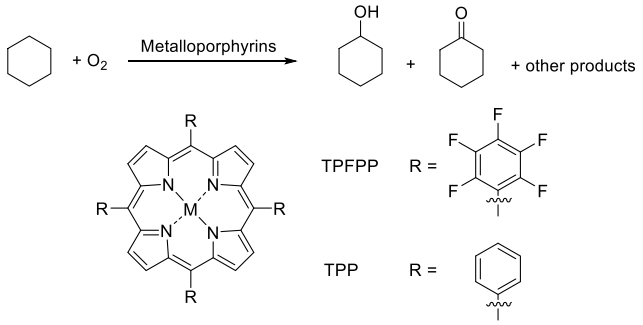
Scheme 22. *Assembly of the porphyrin ring.*

Several oxygen atom donors have been used for the development of efficient P450 biomimetic oxidation systems, the first ones being iodosylarenes, hypochlorites and *N*-oxides, which only contain one oxygen atom and are well-adapted for the selective formation of metal-oxo intermediates.[77] Iodosylbenzene and iodobenzene acetate are commonly used oxygen carriers for metalloporphyrin-mediated oxidation, and additives to prevent catalyst oxidative destruction, such as imidazole, are also used.[81]

Many systems have used O_2 as the oxygen atom source with Mn or Fe porphyrin catalysts. These systems also use a reducing agent, such as sodium borohydride,[82] ammonium borohydride, H_2 in the presence of colloidal platinum, NADH analogues, ascorbate, Zn powder, Zn amalgam and aldehydes.[77] For example, Murahashi *et al.* found that the aerobic oxidation of different alkanes, using cobalt, manganese and ruthenium porphyrins with *meso*-pentafluorophenyl groups afforded alcohols and ketones with high efficiency (Table 4).[83]

A system based on Ru-porphyrin has also applied molecular oxygen without a reductant for the epoxidation of olefins, where the transfer of two oxygen atoms of O_2 to the alkene substrate takes place.[84]

An example of another metalloporphyrin-mediated oxidation reaction without the use of reductants has been accomplished by Guo *et al*., who used simple iron, manganese and cobalt porphyrins to catalyse cyclohexane oxidation with air (Scheme 23). In their reaction, the catalytic activity of cobalt was greater than that of iron or manganese (Table 5).[85]



Scheme 23*. Oxidation of cyclohexane with metalloporphyrins and oxygen.*

Table 4. Metalloporphyrin-catalysed oxidation of cyclohexane with molecular oxygen in the presence of acetaldehyde.

No.	*Catalyst*	*Yields* (%)*			*Turnover number*
		Alcohol	**Ketone**	**Total**	
1	Co(TPFPP)	11	64	75	1.70×10^4
2	Mn(TPFPP)Cl	9.4	61	70	1.59×10^4
3	Ru(TPFPP)(CO)	8.1	54	62	1.41×10^4

*Determined by GLC analysis based on the starting acetaldehyde using an internal standard. It was assumed that 2 moles of aldehyde were necessary for ketone formation.[83]

Table 5. Metalloporphyrin-catalysed oxidation of cyclohexane with molecular oxygen without additional solvents or reductants.

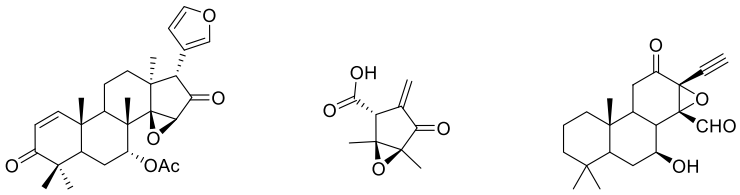
	Co(TPP)	*Mn(TPP)*	*Fe(TPP)*
Cyclohexane conversion (%)	15.0	11.9	8.54
Yields of alcohol and ketone (%)	75.6	73.4	65.1
Time until the yield maximum (h)	1.5	2.5	3.5
Ratios of alcohol to ketone	0.91	0.97	0.94
Catalyst mole turnover number	33937	26289	18866

While metalloporphyrins have been extensively studied over the past decades, limitations still exist in terms of reactivity, selectivity and suitable substrates. Also, the synthesis of the porphyrin cycle remains a challenge for synthetic chemists.

1.2 Oxidation products as sources for natural and bioactive compounds

1.2.1 Epoxides and their derivatives

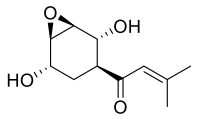
The cyclic epoxide moiety is a motif commonly found in different natural and bioactive compounds (Figure 6). For an example of cyclopentane epoxides, limonoids and their analogues, such as nimbinim **7,** have anti-HIV activity.[86] Another example is the cyclopentenone antibiotic methylenomycin A **8**, which was isolated from the *Streptomyces* bacteria.[87] A representative of cyclohexane epoxides is Escobarine A **9**, a cassane diterpene found in the roots of *Calliandra californica,* which is used in herbal medicine and has shown significant inhibitory-growth activity against *M. tuberculosis.*[88]



7 **8** **9**

Figure 6. *Examples of bioactive epoxides.*

There are different methods to synthesise epoxides. For example, in the synthesis of Eutypoxide B (Figure 7), the different approaches of obtaining the epoxide moiety used were oxidation with mCPBA,[89,90] *t*BuOOH with Triton B in THF[91] or 30% aq. H_2O_2 with Triton B.[92]

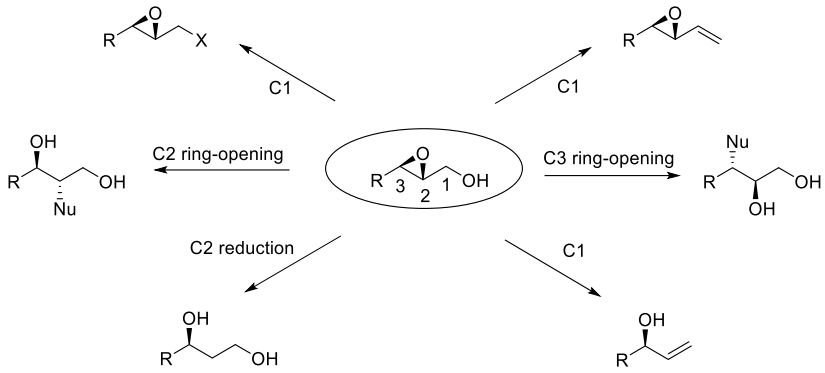


(±)-Eutypoxide B

Figure 7. *Eutypoxide B.*

The use of hydrogen peroxide and peracids for the direct oxidation of alkenes is the main method for industrial applications. Some of them use the directing effect of an allylic alcohol moiety, and some are enantioselective.

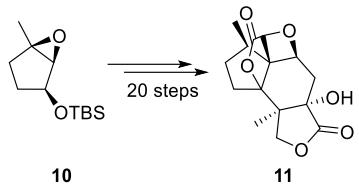
Since epoxides are very versatile in their functionality, it is possible for synthetic chemists to use them for regio- and stereoselective ring opening, oxidation, reduction, *etc*.[37] Generally, the epoxide ring opening reactions can be either functional group transformations of the hydroxyl group, olefination at C1, deoxygenation to an allylic alcohol, reduction at C2 or epoxide opening at C2 or C3 (Scheme 24).[93]



Scheme 24. *Reactions of epoxy alcohols.*

The most common C1 transformations are oxidation to an aldehyde, halogenation and esterification. The reaction of epoxy alcohols with carbon nucleophiles, such as cuprates, leads to an epoxide opening at C2 with moderate regioselectivity. An epoxide opening at C3 yields 1,2-diols as products and the reagents used for this can be trimethylaluminium, oxygen, sulfur or nitrogen nucleophiles.[93]

Chiral epoxy alcohols, such as **10,** are also powerful and effective starting materials and intermediates in the synthesis of important compounds,[93] for example jiadifenolide **11** (Scheme 25), which is a potent neurotropic agent scarce in nature (1.5 mg per kg of *Illicium jiadifengpi* plant).[94]



10 **11**

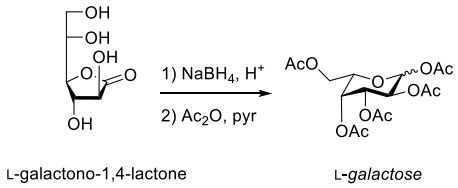
Scheme 25. *Synthesis of jiadifenolide starting from a chiral epoxy alcohol.*

Since epoxides offer various further transformations and also are included in the composition of numerous natural compounds, the ongoing development of their synthesis is necessary. The enantioselective synthesis of epoxides is also of great importance.

1.2.2 Lactones

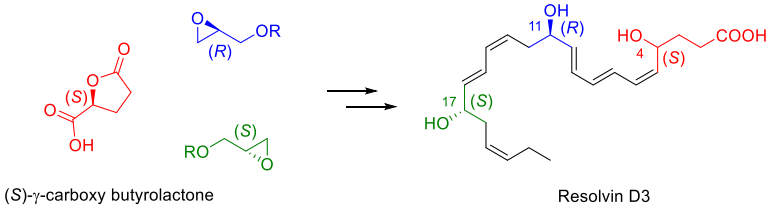
Gamma lactones are five-membered heterocyclic structures found in natural and bioactive compounds. Optically active γ-butyrolactones are a prominent class of chiral building blocks and numerous transformations can be performed on them because of the highly versatile functional group in the furanone structure. Because of these properties, the development of asymmetric synthetic strategies to assemble these compounds has attracted a great deal of attention among synthetic chemists.[95]

Some L-lactones are commercially available and can be transformed into highly valuable L-sugars. For example L-galactono-1,4-lactone, which is a by-product of sugar production, can be used to prepare peracetylated L-galactose (Scheme 26).[96]

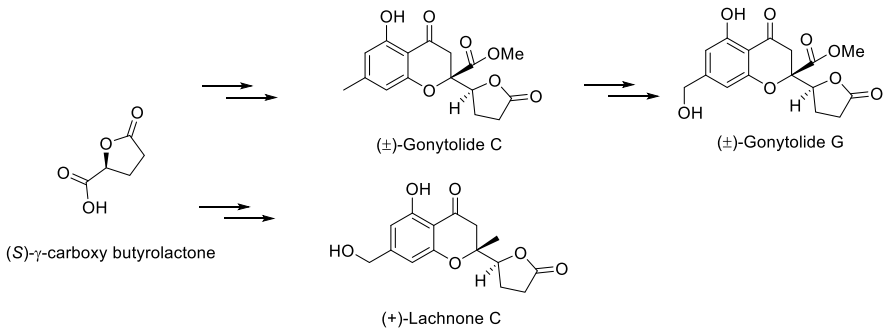


Scheme 26. *Synthesis of an L-sugar from an L-lactone.*

Commercially available (*S*)-γ-carboxy butyrolactone can be used in the synthesis of resolvin D3, a potent anti-inflammatory and pro-resolving lipid mediator (Scheme 27).[97] Lactone carboxylic acids can also be used for the total synthesis of a γ-lactone motif containing the natural products gonytolide C and G and lachnone C (Scheme 28).[98]

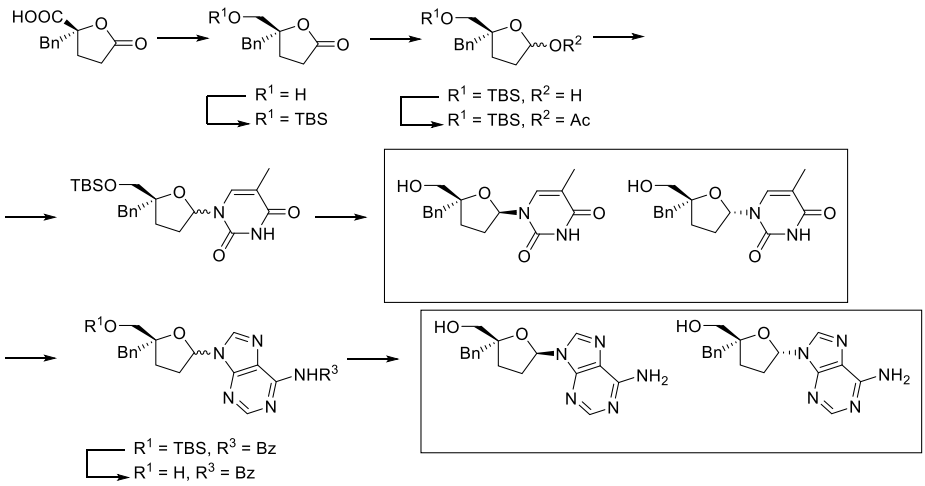


Scheme 27. *Total synthesis of resolving D3 based on enantiomerically pure starting materials.*



Scheme 28. *Total synthesis of lactone motif containing natural products.*

It is also possible to obtain biologically active nucleoside analogues from lactones (Scheme 29). The method is suitable for the synthesis of nucleoside analogues with different alkyl substituents, which allows for the changing of the lipophilicity of the substituents and the achieving of the best antiviral and anticancer properties of the analogue.[99]



Scheme 29. *Synthesis of 4' -benzyl substituted nucleoside analogues.*

There are different ways to synthesize lactones and lactone acids for further transformations. For example, the above-mentioned Baeyer-Villiger reaction of cyclobutanones and oxidative cleavage and cyclization yields lactones and lactone carboxylic acids, depending on the substrate for the cyclization. Furanone derivatives can also be used as nucleophiles to obtain lactones with such reactions as an asymmetric Mukaiyama aldol reaction using a pyridinebis(oxazolinyl) Cu(II) complex as a catalyst.[100] The future of the synthesis of biologically important gamma lactones as for other compounds involves the use of more environmentally friendly reagents that eliminate the need for metal catalysis.

2 Aims of the present work

The general aim of the present work was to investigate the asymmetric oxidation of substituted 1,2-cyclopentanediones and find conditions for the selective formation of different synthetically useful oxidation products.

Specific aims:

- to elucidate the possibility and find conditions for the non-stoichiometric catalytic oxidation of substituted 1,2-cyclopentanediones, in order to increase the efficiency and practical usefulness of the process.
- to elucidate the conditions and characteristics of competitive Sharpless epoxidation and enolate epoxidation of 4-hydroxy-substituted cyclopentane-1,2-diones.
- to broaden the scope of use of the Sharpless complex to the kinetic resolution of epoxides, by studying the resolution of epoxyalcohols in order to obtain enantiomerically enriched products that cannot be achieved by using the Sharpless kinetic resolution of allylic alcohols.
- to broaden the scope of oxidation catalysts for the oxidation of 3-substituted cyclopentane-1,2-diones by using organocatalysts and metalloporphyrins.

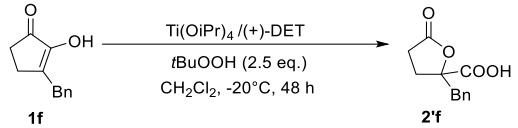
3 Results and discussion

3.1 Asymmetric oxidation of 3-alkyl-substituted cyclopentane-1,2-diones

3.1.1 Catalytic oxidation of 3-alkyl-substituted cyclopentane-1,2-diones (Publication I)

The asymmetric oxidative cleavage of cyclopentane-1,2-diones with titanium isopropoxide/diethyl tartrate/*t*BuOOH catalytic complex resulting in enantiomeric lactone carboxylic acids is well documented.[45,46,47,48,49] The reaction proceeded by using a stoichiometric amount of the Ti-catalyst. Now we have developed conditions for a non-stoichiometric process.

3-benzyl-cyclopentane-1,2-dione **1f** was chosen as the model substrate to find limits for the catalyst amount reduction without substantial loss of yield or enantioselectivity. (Scheme 30; Table 6).



1f **2'f**

Scheme 30*. Oxidation of **1f** with the Sharpless complex.*

The Ti/substrate ratio was reduced from 1 to 0.1, while the amount of oxidizer *t*BuOOH remained the same and based on previous experiments the ratio of Ti/tartaric ester was kept at 1/1.6. It was very clear that the reduction of the complex amount affected the yield and *ee* values, decreasing both. An especially big effect was observed when the ratio of Ti/substrate was reduced to 0.1 (Table 6, No. 7). However, the important finding was that with 0.2 equivalents of the Ti reagent towards substrate, both the yield and *ee* values remained noticeably high (Table 6, No. 6), and at 0.3 Ti/substarte ratio the results were even slightly better (Table 6, No. 4 and 5).

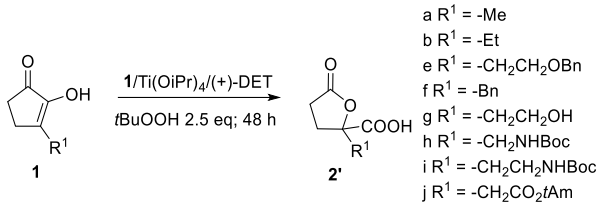
Table 6.[a] Oxidation of 3-benzyl cyclopentane-1,2-dione 1f with Ti/tartaric ester complex and *t*BuOOH at different Ti/substrate ratios.

No.	*Ti(OiPr)$_4$ (eq)*	*(+)-DET (eq)*	*tBuOOH (eq)*	*Yield (%)*	*ee[d] (%)*
1	1	1.6	2.5[b]	83	96
2	0.5	0.8	2.5[b]	78	93
3	0.5	0.1	2.5[c]	42	25
4	0.3	0.48	2.5[b]	71	91
5	0.3	0.48	2.5[c]	72	93
6	0.2	0.32	2.5[c]	69	91
7	0.1	0.16	2.5[b]	26	68

[a]Substrate amount 1 mmol
[b]*t*BuOOH contains ~4% water
[c]anhydrous *t*BuOOH was used
[d]*ee* determined by chiral HPLC

To prove the scope of the developed method the yields and *ee* values of the oxidation of 3-alkyl substrates with different functional groups in the chain by using stoichiometric and catalytic (Ti/substrate ratio 0.3) protocols were compared (Table 7).

Table 7. Oxidation of 3-alkyl cyclopentane-1,2-diones with Ti/tartaric ester complex and *t*BuOOH.

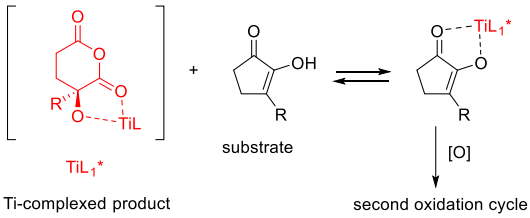


No.	*Substrate 1*	*R*	*Lactone acid 2'*			
			Yield (%)		*ee* (%)	
			Stoich.[a]	Cat.[b]	Stoich.[a]	Cat.[b]
1	a	-Me	75	69	94	94
2	b	-Et	72	-	93	-
3	e	$-CH_2CH_2OBn$	71[c]	69	95	94
4	f	-Bn	83[c]	72	96	93
5	f[c]	-Bn	62[c]	63	92	91
6	f[d]	-Bn	-	68	-	92
7	g	$-CH_2CH_2OH$	80[e]	75[f]	95	90[f]
8	h	$-CH_2NHBoc$	47	38	98	92
9	i	$-CH_2CH_2NHBoc$	69	66	98	92
10	j	$-CH_2CO_2tAm$	-	58	-	94

[a]Ratio of substrate/Ti(O*i*Pr)$_4$/(+)-DET/*t*BuOOH 1:1:1.6:2.5; reaction time 48 h
[b]Ratio of substrate/Ti(O*i*Pr)$_4$/(+)-DET/*t*BuOOH 1:0.3:0.5:2.5; reaction time 48 h
[c]Reaction time 2 h
[d]Reaction time 4 h
[e]Spirodilactone was obtained
[f]*t*BuOOH contained 4% of water

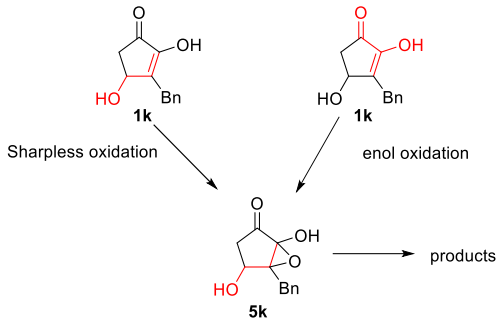
From the data of Table 7, one can conclude that the oxidation reaction tolerates a wide variety of substrates. The catalytic conditions are also mostly suitable. Only substrate **1h** led to poor results.

It was previously found that Ti species participate in all steps of the cascade, catalysing not only the oxidation but also the epoxide re-arrangement and acylation reactions.[49] Titanium is complexed to both the products and the reagent in this reaction. The possibility of a catalytic process hints at the equilibrium between Ti/product and Ti/substrate (Scheme 31), which is an important piece of knowledge for future oxidation reactions with similar substrates.



Scheme 31. Prerequisite for the catalytic oxidation process.

An interesting problem arises from the possible oxidation of 4-hydroxy compounds, which can act as substrates for different processes: a Sharpless oxidation of allylic alcohols, enol oxidation and both (Scheme 32).

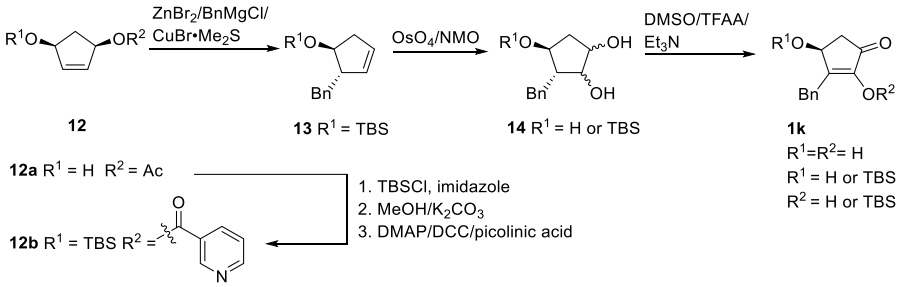


Scheme 32. Possible pathways of oxidation of 4-hydroxy substrate **1k**.

To investigate this reaction, 4-hydroxysubstituted substrate **1k** was synthesized and its oxidation was studied in more detail.

3.1.2 Synthesis of 3-benzyl-4-hydroxy-substituted cyclopentane-1,2-dione 1k

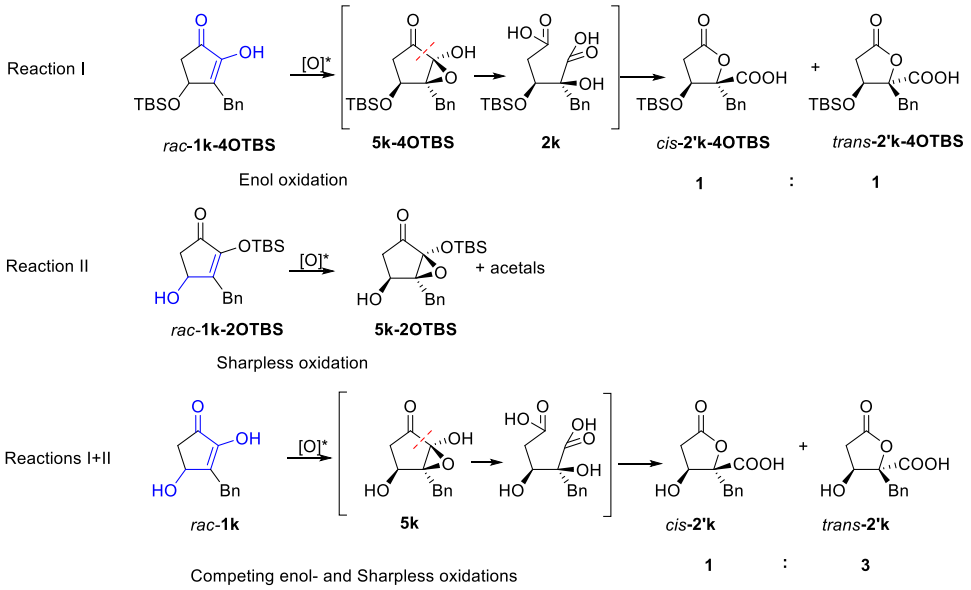
The synthesis of 3-benzyl-4-hydroxy-substituted cyclopentane-1,2-dione **1k** started from cyclopent-2-ene-1,3-diol monoacetate **12**. The ester group acts as a leaving group in an anti S_N2' reaction with a Grignard reagent (*via* R-ZnBr) in the presence of a Cu catalyst[101] to afford a benzyl-substituted cyclohexene **13** with a hydroxyl moiety. The use of a picolinyl ester as the leaving group instead of the acetate group affords almost exclusive *trans*-selectivity.[102] After dihydroxylation to diol **14** and modified Swern oxidation, [103] the expected product **1k** was obtained (Scheme 33).



Scheme 33. *General scheme of the synthesis of 3-benzyl-4-hydroxysubstituted cyclopentane-1,2-diones.*

3.2 Oxidation of 3-benzyl-4-hydroxy-substituted cyclopentane-1,2-dione 1k

To understand the selectivity of the possible oxidation reactions, differently protected substrates **1k** were prepared and their asymmetric oxidation using a Ti/tartaric ester/*t*BuOOH complex was studied (Scheme 34, Table 8).



Scheme 34. Oxidation pathways of substrates **1k.**

Table 8.[a] Oxidation of 4-hydroxy 3-benzyl cyclopentane-1,2-diones with a Ti/tartaric ester/*t*BuOOH complex.

No.	*Substrate*	*Product* *Yield (%)/ee (%)*		*Total yield, (%)*	*dr[d]*
1	*rac*-**1k-4OTBS**	*cis*-**2'k-4OTBS** 27/95	*trans*-**2'k-4OTBS** 27/97	54	1:1
2	*rac*-**1k-4OTBS**[b]	*cis*-**2'k-4OTBS** 26/95	*trans*-**2'k-4OTBS** 26/95	52	1:1
3	*rac*-**1k-2OTBS**	*cis*-**5k-2OTBS** 41/48	Not detected	41	>20:1[c]
4	*rac*-**1k**	*cis*-**2'k** 33/80	*trans*-**2'k** 11/70	44	3:1

[a]Substrate/Ti(O*i*Pr)$_4$/(+)-DET/*t*BuOOH 1/1/1.6/2.5; CH_2Cl_2, –20°C, reaction time 48 h
[b]Catalytic; substrate/Ti(O*i*Pr)$_4$/(+)-DET/*t*BuOOH 1/0.3/0.5/2.5; CH_2Cl_2, –20°C, reaction time 48 h
[c]Only one diastereomer detected
[d]Determined by NMR of isolated product

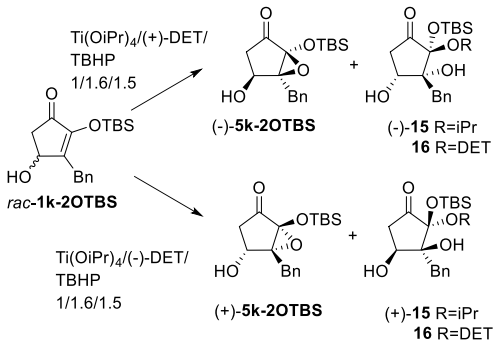
The asymmetric oxidation of *rac*-4-hydroxyl-protected diketone *rac*-**1k-4OTBS** proceeded *via* Pathway I and provided *cis*- and *trans*-diastereomers in 1:1 ratio with excellent enantioselectivity for both diastereomers (Table 8, No. 1). With this substrate, the catalytic conditions also afforded almost the same yield and selectivity as with a stoichiometric catalyst amount (Table 8, No. 2).

With 2-protected substrate *rac*-**1k-2OTBS,** only a Sharpless oxidation occurred (Pathway II) and, as expected, allylic epoxide *cis*-**5k-2OTBS** was isolated in 41% yield. The enantioselectivity of the Sharpless oxidation of cyclic alkenes is moderate[5] and we also obtained only 48% *ee* (Table 8, No. 3). In the case of enol oxidation (pathway I) the initial step was also epoxidation. However, in this case the formed initial hydroxy epoxide **5k-4OTBS** was very unstable and immediately trasformed further.[104] The finding of the possibility of isolating a stable epoxide *cis*-**5k-2OTBS,** which might be a valuable chiral intermediate, led us to further investigation of its chemical properties (Chapter 2.2).

With all-unprotected substrate *rac*-**1k** where both pathways – enol oxidation and Sharpless oxidation – were possible and competing, the ring cleaved products *cis*-**2'k** and *trans*-**2'k** were obtained in 44% total yield with a 3:1 ratio of *cis*/*trans* isomers (Table 8, No 4). The enantioselectivity of the process was considerably lower than that for Reaction I and higher than that for Reaction II, which suggests that the rates of enol oxidation and Sharpless oxidation of the substrate were comparable.

3.2.1 Epoxidation of 3-benzyl-4-hydroxy-substituted cyclopentane-1,2-dione (Publication II)

With the protected enol 2-OH group of the 3-benzyl-4-substituted cyclopentane-1,2-dione, the substrate acted as an allylic alcohol and oxidised according to Sharpless allylic oxidation (Scheme 34, Reaction II). This gave the opportunity to use Sharpless kinetic resolution of *rac*-**1k**-**2OTBS** to obtain the enantiomerically enriched substrate **1k-2OTBS** and also the enantiomerically enriched epoxyalcohol **5k-2OTBS** (Scheme 35).



Scheme 35**. Sharpless epoxidation of **1k-2OTBS.

The first kinetic resolution with $Ti(OiPr)_4$/(+)-DET gave epoxide (–)-**5k-2OTBS** in 29% yield with 46% *ee*, isopropyl acetal (–)-**15** in 7% yield and 14% *ee*, and diethyl tartrate acetal **16** in 21%. The *ee* value of the recovered substrate **1k-2OTBS** was only 16% (Table 9, No. 1). The experiment was repeated with (–)-DET and the results differed

considerably. The reaction with (–)-DET resulted in epoxide (+)-**5k-2OTBS** in 26% yield and 74% *ee*, isopropyl acetal (+)-**15** in 8% yield and 54% *ee*, and diethyl tartrate acetal **16** in 18% yield; no unreacted substrate was recovered from this reaction (Table 9, No. 2). The obtained result that (+)-DET and (–)-DET) gave different stereoselectivity values for (–)-**5k-2OTBS** and (+)-**5k-2OTBS** (46% and 74% *ee*, respectively) was surprising and emphasised the sensitivity of the reaction.

The experiments with racemic substrate were repeated but the variations remained. (Table 9, No. 3 and 4). In all cases, together with the epoxide, acetals **15** and **16** formed. However, the variations in the epoxide/acetals ratio was also surprising. It was noteworthy that for both compounds (epoxide and acetal) the formation of only one diastereomer was observed.

Table 9[a] Initial results for the kinetic resolution of *rac*-1k-2OTBS (Scheme 35).

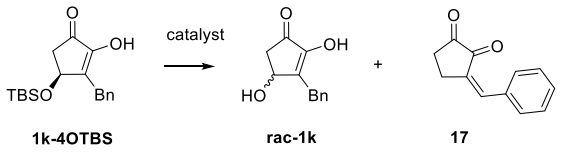
No.	*DET*	*5k-2OTBS yield (%)/ee (%)*	*15 yield (%)/ee (%)*	*16 yield (%)*	*Unreacted 1k-2OTBS Yield (%)/ ee (%)*
1	(+)	(–); 29/46	(–); 7/14	21	(–); 12/16
2	(–)	(+); 26/74	(+); 8/54	18	-
3	(–)	(+);48/38	(+); 2/52	13	(+); 37/2
4	(+)	(–); 36/38	(–); 2/62	19	(+); 27/6

[a]Reaction duration 1 day

With these initial results, it was necessary to understand the reasons for differences of obtained stereoselectivities.

We started to solve the first problem by using the enantiomerically enriched substrate **1k-2OTBS** for oxidation to take advantage of the formation of "matched/mismatched" pairs with different DET enantiomers in the reagent complex.

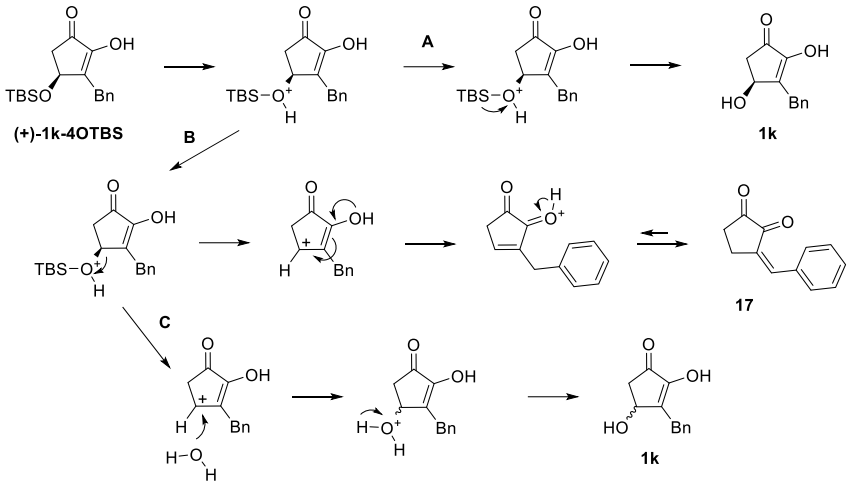
The enantiomerically enriched substrate **1k-2OTBS** was prepared starting from enantiomeric cyclopentene diol monoacetate **12a** (prepared by deacetalization of cyclopentene-1,4-diacetate with enzyme Novozym SP 435™)[105] according to Scheme 33. Unfortunately, it was found that the removal of the 4-hydroxyl protecting group in **1k-4OTBS** with HCl, TBAF, HFxPy and AcOH racemised the product. (Scheme 36).



1k-4OTBS **rac-1k** **17**

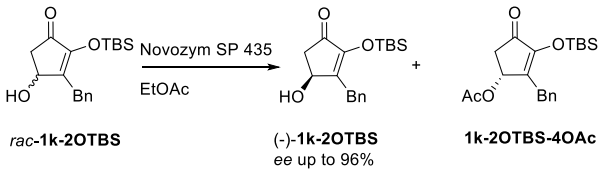
Scheme 36. *Racemisation of **1k-4OTBS** during deprotection.*

It is possible to rationalise the racemisation as presented in Scheme 37, suggesting that racemisation occurs by forming a carbocation as an intermediate as one option. This assumption is supported by the formation of compound **17**.

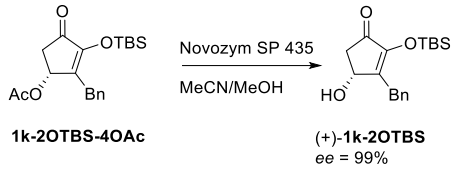


Scheme 37. *Rationalisation of racemisation during deprotection of* ***1k-4OTBS****.*

So we had to choose another route by using the enzyme Novozym™ in the acylation of diketone *rac*-**1** (Scheme 38) and for the other enantiomer, Novozym using the deacylation of the obtained product (Scheme 39).[106]



Scheme 38. *Acylation reaction with Novozym enzyme.*



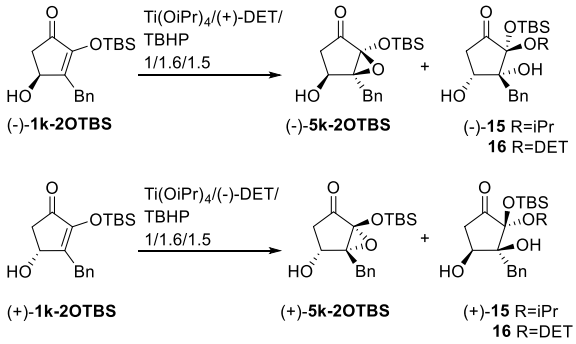
Scheme 39. *Deacylation reaction with Novozym enzyme.*

With these enantiomerically enriched substrates, the epoxidation reaction was repeated with the substrate/reagent (+)/(—) and (—)/(+) combinations (Table 10) and also with the substrate/reagent (—)/(—) and (+)/(+) combinations (Table 11).

In Table 10 it is seen that when the *ee* of the substrate is high, it is possible to get epoxides with high *ee* values from cyclic allylic alcohols (Nos. 1, 2 and 3). When the reaction time was increased to 3 days, the *ee* of the resulting epoxide was 90% and the

ee of the remaining substrate was 84% (Table 10, No. 2). It is noteworthy that in these experiments the acetals **15** and **16** were not detected.

Table 10.[a] Epoxidation of enantiomerically enriched substrate 1k-2OTBS by using substrate/DET (+)/(—) and (—)/(+) pairs.



No.	*DET*	*Substrate; ee (%)*	*Products*			
			Remaining substrate; Yield (%)/ *ee* (%)	**5k; yield (%)/*ee* (%)**	**15; yield (%)/*ee* (%)**	**16**
1	(+)	(–);88	(–); 59/88	(–); 31/88	-	-
2[b]	(+)	(–); 88	(–); 35/84	(–); 45/90	-	-
3	(–)	(+); 99	(+); 32/99	(+); 54/99	-	-
4[c]	(+)	(–); 12	(–); 35/nd	48, *ee* nd	2/nd	16
5[c]	(–)	(+); 74	(+); 32/82	(+); 63/92	1/nd	4
6[c]	(+)	(–); 92	(–); 41/nd	(–); 55/96	1/nd	2

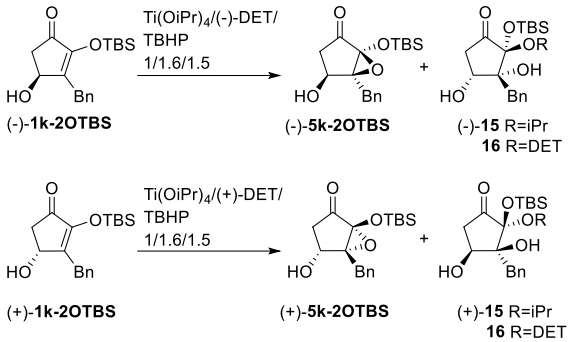
[a]Reaction duration 1 day, all *ee* values obtained from chiral HPLC analysis of isolated products
[b]Reaction duration 3 days
[c]Conversions from RP-HPLC

With the substrates of lower enantiomeric purity, the acetals appeared together with epoxides as reaction products in isolatable amounts (direct HPLC analysis of the product). It was clear that with a substrate with moderate *ee* value, acetals had formed in considerable amounts (Table 10, No. 4 and 5) and with a substrate of very high *ee* value, there was only very small amounts of acetals formed (Table 10, No. 6).

For the substrate/DET (+)/(+) and (—)/(—) pairs with substrate *ee* value 88%, no separable amounts of acetals formed (Table 11, No. 3). Also the *ee* of the substrate remained unchanged during the reaction. The epoxide formed from the reaction had 82% *ee*. This slight decrease in epoxide *ee* hinted at some chance of a different occurring reaction than just epoxidation.

After repeated experiments with the substrate, the *ee* values were 94% (Table 11, No. 1) and 96% (Table 11, No. 2). It was seen that the *ee* value of the substrate had remained the same but the HPLC technique also made it possible to detect acetals.

Table 11.[a] Epoxidation of enantiomerically enriched substrate 1k-2OTBS by using substrate/DET (+)/(+) and (—)/(—) pairs.



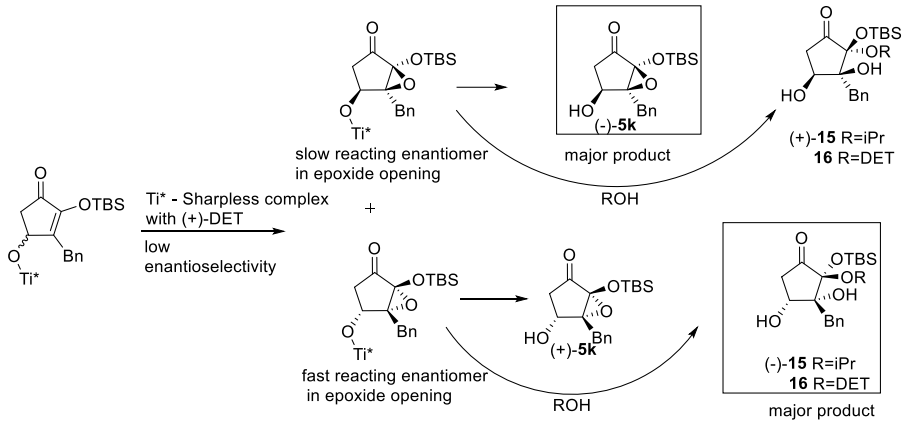
No	*DET*	*Substrate; ee (%)*	*Products*			
			Remaining substrate; yield (%)/*ee* (%)	**5k yield (%)/*ee* (%)**	**15 yield (%)/*ee* (%)**	**16**
1	(+)	(+); 94	(+); 52/99.5	(+); 35/100	(–); 1/90	12
2[b]	(–)	(–);96	(–); 36/96	(–); 38/90	(–); 2/98	24
3[b]	(–)	(–);88	(–);53/88	(–); 19/82	-	-

[a]Reaction duration 1 day, all *ee* values obtained from chiral HPLC analysis of isolated products
[b]Conversions from RP-HPLC

3.2.2 Kinetic resolution and mechanism of oxidation: rationale of the reaction behaviour

When oxidizing the enantiomerically enriched substrates, we obtained epoxides with higher *ee* values, but these values also varied. The most striking effect was that the amount of different formed products depended on the enantiomeric purity of the starting substrate. When the *ee* value of the substrate was over 90% and there was a (—)/(+) and (+)/(—) situation, and an arbitrary "match" case complex for the substrate was used (Table 10, No. 6), the amount of formed acetals was very low (3%). However with the (—)/(—) and (+)/(+) situations, an arbitrary "mismatch" situation (Table 11, No. 1 and 2), more acetals had formed in the same time (13% and 26%, respectively).It could clearly be seen that when the match pair was used (either (—)-**1k-2OTBS** and (+)-DET or (+)-**1k-2OTBS** and (—)-DET), the reaction followed this rule: when the *ee* of the substrate was high, the reaction proceeded via the epoxidation reaction and yielded an epoxide with approximately the same *ee* value as that of the substrate. When the substrate *ee* was lower, the *ee* value of the epoxide changed considerably compared with that of the substrate, and more acetals formed.

On the basis of the obtained results, the reaction can be rationalised as proposed in Scheme 40.



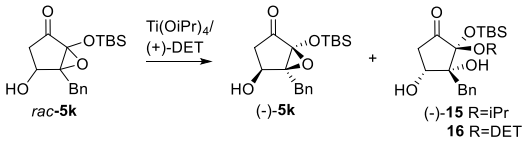
Scheme 40. *Rationalisation of the subsequent kinetic resolutions.*

It can be seen that in the first reaction the epoxidation occurred with low enantioselectivity (as reported before; the rate of formation of different enantiomers was still considerably different). In the next reaction, acetal formation from epoxyalcohol was highly stereoselective and could occur either with *i*PrOH or DET. This also explains why there were more acetals in the case of a noticeable change in the epoxide *ee* value compared with the substrate *ee* value and changes in the product profile depending on the substrate *ee* value. The obtained result, that the epoxide opening of **5k** is stereoselective, opens up the possibility of using it in the kinetic resolution of epoxides.

3.2.3 Kinetic resolution of epoxide 5k

To test the suggestion of a possible kinetic resolution of epoxides, racemic epoxyalcohol **5k** was synthesised and subjected to the $Ti(OiPr)_4$/(+)-DET solution (Table 12). After one day almost half of the starting compound **5k** was consumed, and 33% of acetals (—)-**15** and **16** had formed. The stereoselectivity of the process was moderate, affording (—)-**5k** with 60% *ee*, and acetals (—)-**15** with 50% *ee* and acetal **16** as a single enantiomer. After four days, the *ee* of the remaining epoxide (53%) had increased to 96%, with the total yield of the epoxide opening products acetals **15** and **16** having increased to 47%

Table 12.[a] Kinetic resolution of epoxyalcohol 5k.

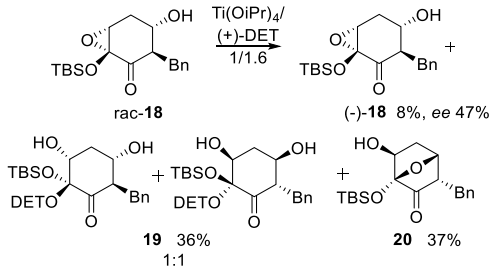


Time	*(—)-5k; Yield (%)/ ee (%)*	*(—)-15 Yield (%)/ee (%)*	*16, Yield (%)*
1 day	66/ 60	4/ 50	29
4 days	53/ 96	10/ 12	37

[a]Reaction conditions: sub./Ti(O*i*Pr)$_4$/(+)-DET 1/1/1.6; CH_2Cl_2, -20°C. All *ee* values are obtained from chiral HPLC analysis of separated products. Product conversion is calculated through RP-HPLC.

The obtained results confirm that the Sharpless complex can be used for the kinetic resolution of the epoxide derivatives of 1,2-cyclopentanediones.

We made an attempt to broaden the scope of this kinetic resolution approach to other epoxides. For that purpose, cyclohexyl homoallylic alcohol epoxide (derived from cyclohexane-1,2-dione) *rac*-**18** was subjected to kinetic resolution (Scheme 41). The kinetic resolution of epoxyalcohol *rac*-**18** gave the following results: (—)-**18** was obtained in 47% *ee* when ~90% of the epoxide was consumed. DET-acetals **19** (diastereomeric ratio 1:1) and **20** were formed in 36% and 37% total yield, respectively.



Scheme 41. *Kinetic resolution of rac-**18.***

Then, since the achieved results for obtaining enantiomerically enriched epoxide were insufficiently selective, we turned our attention to metalloporphyrins and H-bond forming organocatalysts for the oxidation of 1,2-diketones.

3.3 Attempts to find a new oxidation catalyst

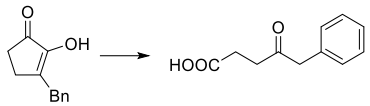
3.3.1 Oxidation with organocatalysts (unpublished results)

Hydrogen-bond mediated organocatalysis was employed for enantioselective oxidation reactions.[64,65,66,67] We checked the possibility of obtaining epoxides from 3-substituted cyclopentane-1,2-diones.

The catalysts chosen for the reaction were a set of known hydrogen-bond organocatalysts: prolinol **XXV**, thioureas **XXVI** and **XXVIII** and squaramide **XVII**. Also, the oxidant was *t*BuOOH, which is a common oxidant used in organocatalysis to obtain

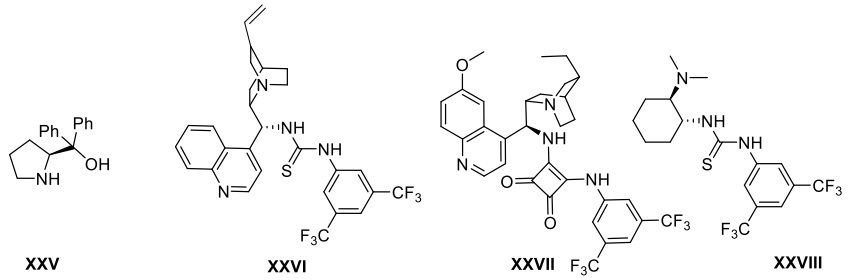
epoxides.[107] The initial reactions used a 0.2 M solution in $CDCl_3$ and *t*BuOOH as the oxidant. The reaction of **1f** with *t*BuOOH in the presence of 20 mol% of the organocatalyst was monitored by ^1H NMR. The obtained results are presented in Table 13.

It was found that the only oxidation product that arose from the reaction was achiral ketoacid **3f.** The formation of epoxide **5f** was not detected with substrate **1f**. (Scheme 42; see also Schemes 43 and 44 in the present chapter). The yield of **3f** varied from 42 to 73% in a 2-day reaction. It is most probable that this reaction proceeds *via* aminocatalysis as in the case of the reaction with electrophiles and diphenylprolinol **XXV** (Gert Preegel *et al*.[108]). However, it may also be possible that the catalyst acts as a hydrogen bond donor. The results are comparable with those of catalysts **XXVI**, **XXVII** and **XXVIII**.



Scheme 42. *Organocatalytic oxidation of **1f**.*

Table 13.[a] Oxidation of 1f by using organocatalyts.



XXV XXVI XXVII XXVIII

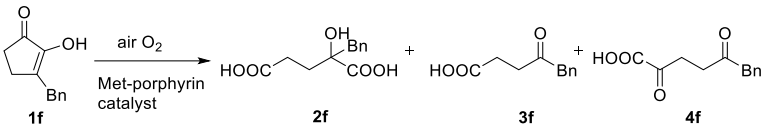
No.	*Catalyst*	*3f after 2 h (%)*	*3f after 1 day (%)*	*3f after 2 days (%)*
1	**XXV**	10	31	49
2	**XXVI**	26	41	42
3	**XXVII**	30	47	73
4	**XXVIII**	24	44	61

[a]Oxidant *t*BuOOH, catalyst loading 20 mol%.

3.3.2 Oxidation with metalloporphyrins (Publication III)

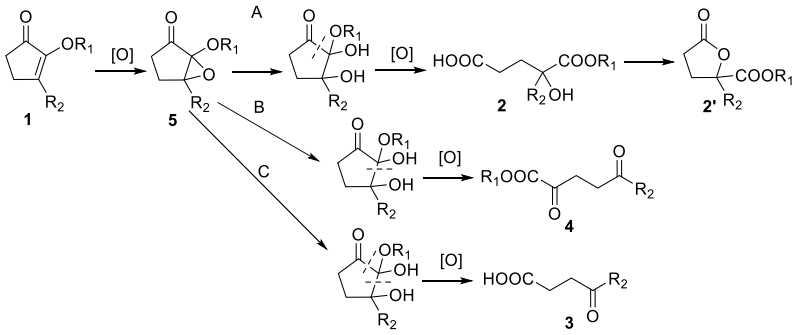
Since these previously obtained results suggested that under organocatalytic conditions epoxide **5** and its derivatives cannot be obtained, we turned to metalloporphyrins in an attempt to find another approach. Although, the aerobic oxidation with metalloporphyrins usually requires an additional reductant, we tried not to use additional reagents.

Our traditional substrate 3-benzyl cyclopentane-1,2-diketone **1f** was chosen as a model compound. We observed the formation of different oxidation products **2**-**4** (Scheme 43).



Scheme 43. *Reaction products of the oxidation of diketone **1f**.*

The formation of the isolated products can be rationalised as presented in Scheme 44.



Scheme 44. *Formation of the reaction products.*

It can be seen in Scheme 44 that epoxidation is the first step of oxidation. This step is followed by an epoxide opening reaction and oxidative ring cleavage process. Of the isolated products, only **2** and **2'** are chiral and may be obtained in an enantiomerically enriched form by asymmetric oxidation reactions.

We had in hands a wide choice of metalloporphyrins (Figure 8; Victor Borovkov). It is known that the oxidation systems with metalloporphyrins are very sensitive to metal, solvent and substrate structures.[109,110] It may be possible that every substrate has only one ideal combination of catalyst structure and reaction conditions.

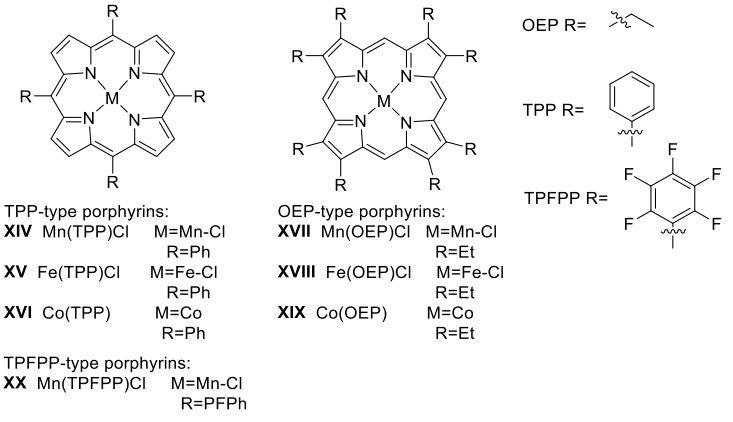


Figure 8. *Metalloporphyrins used.*

The conversion of the substrate was monitored by NMR spectra. The results are presented in Table 14. It was initially found that NMR spectra may give some misleading data, as the protons of diacid **2** and diketoacid **4** are located in similar areas. However, it was observed that the differentiation of these signals could be made from the shape of the chemical shifts of diacid **2** and diketoacid **4** (Figure 9, A and B, respectively).

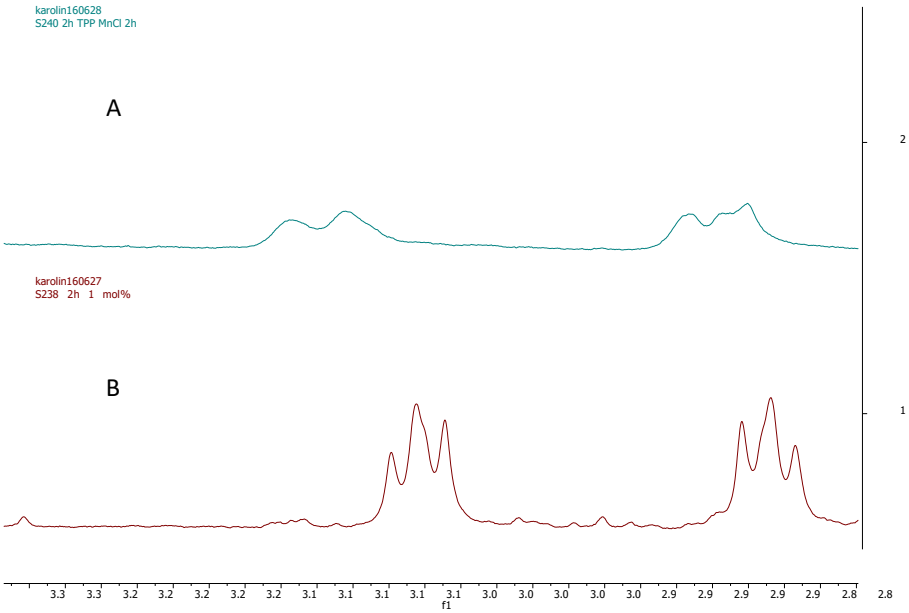
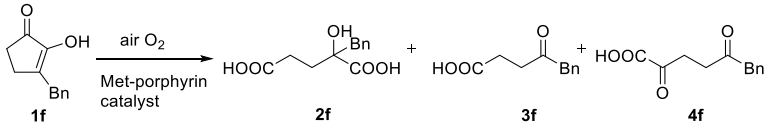


Figure 9. *1H NMR shifts of diacid (A) and diketoacid (B).*

Table 14.[a] Initial catalyst and solvent screening results for oxidation of 1f.

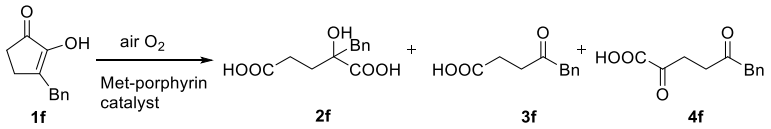


No.	*Catalyst*	*Loading*	*Solvent*	*Time*	*2f (%)*	*3f (%)*	*4f (%)*
1	**XIV**	5 mol%	$CDCl_3$	2h	49	51	-
2	**XV**	5 mol%	$CDCl_3$	2h	-	37	32
3	**XV**	1 mol%	$CDCl_3$	2h	-	24	48
4	**XV**	1 mol%	Toluene	24h	-	41	59
5	**XV**	1 mol%	CH_2Cl_2	2h	-	23	52
6	**XV**	1 mol%	CH_2Cl_2	24h	-	35	58
7	**XV**	1 mol%	THF	24 h	-	24	70
8	**XV**	10 mol%	$CDCl_3$	2h	-	26	40
9	**XVI**	5 mol%	$CDCl_3$	2h	8	24	48
10	**XVII**	5 mol%	$CDCl_3$	2h	33	67	-
11	**XVIII**	5 mol%	$CDCl_3$	2h	-	30	40
12	**XIX**	5 mol%	$CDCl_3$	2h	-	18	33

[a]Conditions: rt. Conversions from crude NMR.

If we consider diacid **2** the target compound, it can be seen that Mn is the best central metal for the porphyrin catalyst in the aerobic oxidation reaction. All other catalysts are too active, causing over-oxidation and the formation of compounds **3** and **4**. When comparing the three Mn-catalysts, we observed that *meso*-TPFPP substituted metalloporphyrin **XX** was much less active: in two hours no conversion proceeded (Table 15, No. 3). Also it was found that the catalyst **XIV** affords the best yields of the product **2f**.

Table 15.[a] Comparison of different Mn porphyrins with the substrate 1f.

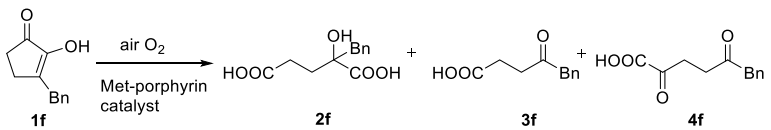


No.	*Catalyst*	*Loading*	*2f (%)*	*3f (%)*
1	**XVII**	5 mol%	33	67
2	**XIV**	5 mol%	54	46
3	**XX**	1 mol%	-	-
4	**XIV**	1 mol%	55	42

[a]Solvent $CDCl_3$, rt, 2h. Conversions from crude NMR.

Since the TPFPP-catalyst **XX** had different characteristics, we screened it under different reaction conditions. The results for oxidation with THF as a solvent are presented in Table 16. We found that the solvent change influenced the oxidation substantially. Of the Mn-catalysts, catalyst **XX** resulted in the best selectivity for products **2** and **3**. However, because the reaction with catalyst **XX** was much slower than with catalyst Mn(TPP)Cl (**XIV**), we continued experiments with Mn(TPP)Cl catalyst **XIV,** as this was experimentally simple, requiring only small amounts of catalyst and using air as the source of oxygen.

Table 16.[a] Conversion of 1f with TPFPP-catalyst XX.



No.	*Time (h)*	*2f (%)*	*3f (%)*
1	2	0	0
2	24	23	0
3	48	87	13

[a]THF; rt; catalyst 1 mol%. Conversions from crude NMR.

When we monitored the kinetics of the formation of products **2** and **3,** we observed S-shape curves for both of them (Figure 10). This might mean that the first step in the reaction is hydrogen abstraction from the enol hydroxyl group of the diketone, which then starts the radical chain for oxidation with dioxygen. The radical nature of the reaction (proven by reaction inhibition upon adding radical scavengers TEMPO and BHT) may cause the formation of a racemic product.

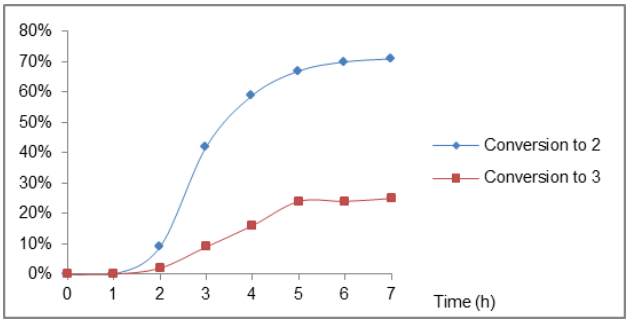
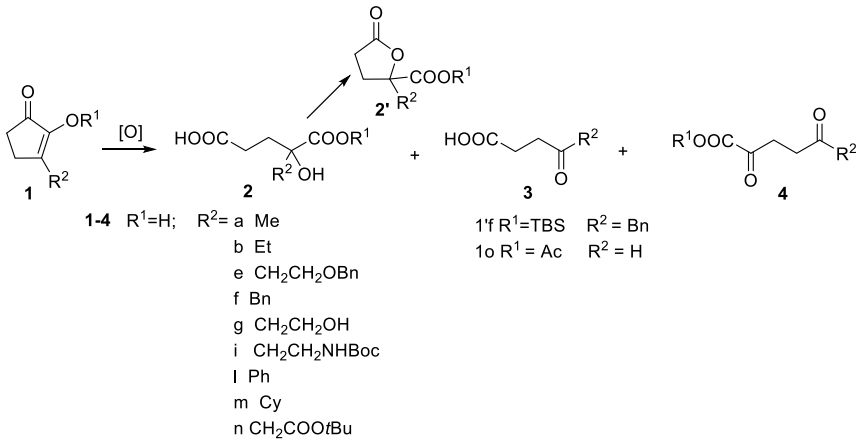


Figure 10. *Reaction kinetic curves for* ***2*** *and* ***3*** *with the catalyst* ***XIV****.*

The scope of the reaction was also studied. The results are presented in Table 17.

Table 17.[a] Substrate scope results.



No.	*Substrate*	*R^1*	*R^2*	*Time*	*2(%)*	*3 or 4 (%)*
1	**1a**	H	Me	24 h	11 (and **2'b** 2)	**3a** 66
2	**1b**	H	Et	48 h	40[b]	**3b** 16[b]
3	**1e**	H	CH_2CH_2OBn	48 h	51[b]	**3e** 43[b]
4	**1f**	H	Bn	18 h	75 (63[b])	**3f** 16 (16[b])
5	**1'f**	TBS	Bn	24 h	-	-
6	**1g**	H	CH_2CH_2OH	48 h	33[b]	-
7	**1i**	H	CH_2CH_2NHBoc	48 h	-	-
8	**1l**	H	Ph	24 h	-	-
9	**1m**	H	Cy	48 h	-	**4m** 86
10	**1n**	H	$CH_2COOtBu$	48 h	-	-
11	**1o**	Ac	H	24 h	-	-

[a]Solvent toluene, rt, 1 mol% Mn(TPP)Cl. Conversions from NMR of crude mixture.
[b]Isolated yield.

On the basis of the obtained results, we see that there are only a limited number of suitable substrates. The structures of investigated structures are presented in Figure 11.

It is clearly seen from Table 17 that electron-donating groups favour the reaction (compounds **1a**, **1b**, **1e**, **1f**, **1g** and **1m**), while electron-withdrawing groups inhibit the reaction (compounds **1l** and **1n**). Also, it is seen that enol-protected substrates (**1'f and 1o**) are not suitable for the reaction. It may also be true that the sterical effect may be important and therefore bulky substituents also inhibit the reaction (substrate **1i**) or influence the product formation (**1m** only gave **4m** as a product under the used conditions).

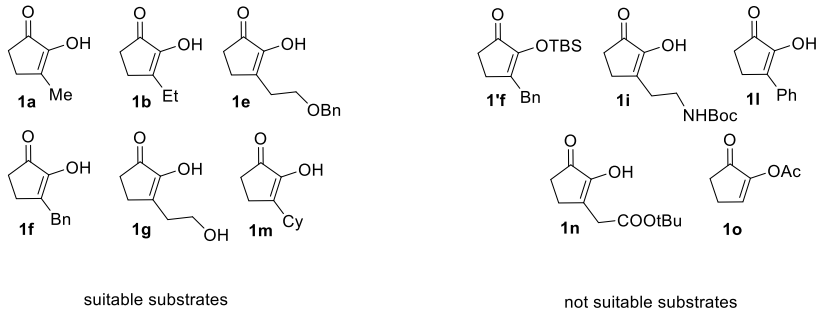


Figure 11. *Substrates **1** for the oxidation with catalyst **XIV**.*

3.3.3 Attempts to achieve enantioselectivity in metalloporphyrin oxidation (unpublished results)

To make the reaction non-radical and see the influence of it on product formation, we used another source of oxygen: PhIO. This oxygen donor has been used extensively with metalloporphyrins and is known to react in a non-radical manner.[109] The chiral and enantiomeric metalloporphyrins (Figure 12; obtained from the groups of Gerard SImonneaux (**XXI** and **XXII**) and Emma Gallo (**XXIII** and **XXIV**)) were used as asymmetric inducers. The results are presented in Table 18.

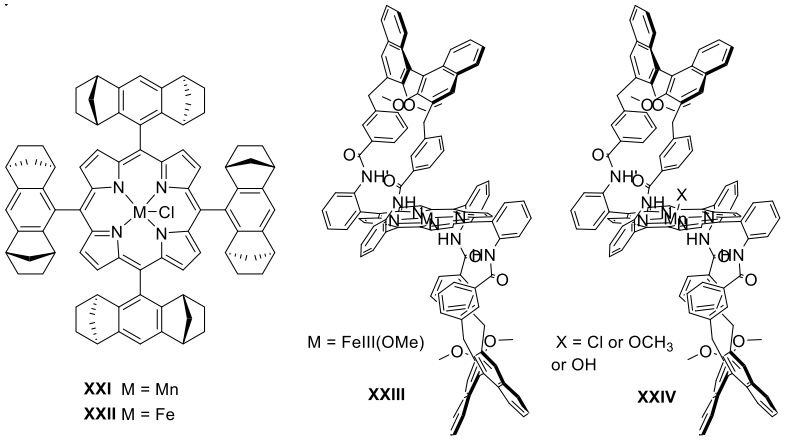
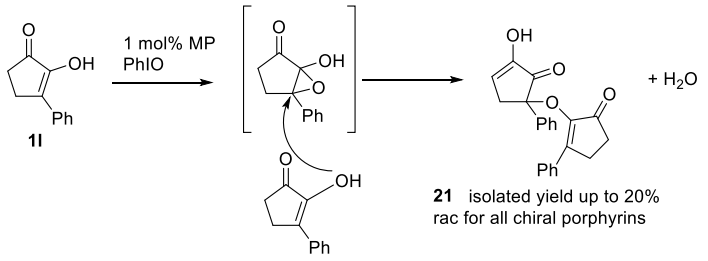


Figure 12. *Chiral metalloporphyrins.*

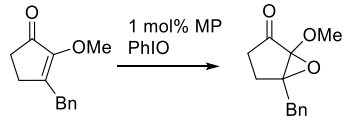
We observed that the use of bulky chiral metalloporphyrin catalysts and the other source of oxygen changed the product profile and substrate reactivities. While with catalyst **XIV** with unprotected Ph-substituted substrate **1l** no reaction occurred, with all catalysts **XXI**-**XXIV** we detected the formation of dimerisation product **21** in up to 20% yield: this means that epoxidation occurred and after epoxidation the formed epoxide reacted with another molecule of the initial substrate **1l** (Scheme 45). With all chiral metalloporhyrins (Figure 12), the reaction was non-stereoselective.



Scheme 455. *Reaction of **1l** with chiral MP and PhIO.*

With methyl-protected diketone **1f-2OMe** (enol-protected diketones were unreactive with non-chiral metalloporphyrins under aerobic conditions), only epoxidation occurred with all metalloporpyrins **XXI**-**XXIV**. The results are presented in Table 18. In most cases, the reaction was non-stereoselective. Only with Fe norbornene-type metalloporphyrin **XXII** 8% *ee* for **5f-2OMe** was observed (Table 18, No. 2).

Table 18.[a] Epoxidation results of 1''f.



No.	*MP*	*Time*	*Conversion to 5f-2OMe (%)*	ee *(%)*
1	**XXI**	4 days	30	0
2	**XXII**	4 days	7	8
3	**XXIII**	4 days	29	0
4	**XXIV**	4 days	48	0

[a]Solvent $CDCl_3$, conversions were measured from crude NMR, *ee* values were determined from chiral HPLC analysis of isolated products.

The possible reason for the lack of stereoselectivity (or very poor selectivity; see Table 18, No. 2) may have been the long distance from the catalyst metal atom to the chiral part of the metalloporphyrin. The cavity size and the reaction mechanism were unclear and therefore it is impossible to draw conclusions at this time. However, even low selectivity obtained in one experiment provided hints of the possibility of controlling reaction selectivity with a selection of proper porphyrin catalysts.

Conclusions

The asymmetric oxidation of substituted 1,2-cyclopentaneones was investigated and conditions for the selective formation of different oxidation products were established. The following features of the oxidation of substituted cyclopentane-1,2-diones were explored and improved:

1) A general method for the oxidation of substituted cyclopentane-1,2-diones by using the Ti-tetraisopropoxide/tartaric ester/*t*BuOOH complex (Sharpless complex) in a non-stoichiometric amount was developed. The ratio of substrate/Ti-species was reduced to 1/0.3 without a significant loss in yields or enantioselectivities.
2) The Sharpless complex was used to oxidise 4-hydroxyl-substituted 3-benzyl-cyclopentane-1,2-dione, resulting in synthetically valuable cyclic epoxyalcohols. The possible reaction pathways and product formation were rationalised.
3) A method for the kinetic resolution of cyclic epoxyalcohols by using a Ti-tetraisopropoxide/tartaric ester/*t*BuOOH complex resulting in enantiomerically enriched epoxyalcohols and its opening products was developed.
4) The reaction pathways by using metalloporphyrin catalysts in the air oxidation of substituted cyclopentane-1,2-diones was elucidated: the reaction proceeded in different extents, with formation variety of oxidation products, depending on the central metal ion of the catalyst.
5) Chiral porphyrins and organocatalysts were tested for the asymmetric oxidation of substituted cyclopentane-1,2-diones. The obtained results showed that the catalysts were non-selective. However, a small asymmetric induction obtained with one chiral metalloporphyrin indicates the possibility of stereoselection using that approach.

4 Experimental

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a 400 MHz instrument. Residual solvent signals were used ($CDCl_3$ δ = 7.26 (^{1}H NMR), 77.16 (^{13}C NMR)) as internal standards. High resolution mass spectra were recorded by using an Q-TOF LC/MS spectrometer by using ESI ionization. Elemental analyses were done by using Elementar vario Micro. Precoated silica gel 60 F254 plates were used for TLC. Column chromatography was performed on a preparative purification system with silica gel Kieselgel 40-63 µm. Purchased chemicals and solvents were used as received. Petroleum ether has a boiling point of 40-60 °C.

(1*S,3*R**,4*S**,6*R**)-3-benzyl-1-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-7-oxabicyclo-[4.1.0]heptan-2-one 18**

The compound was prepared by the procedure described in article II.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.15 (m, 5H), 3.75 – 3.69 (m, 1H), 3.65 – 3.61 (m, 1H), 3.08 – 3.04 (m, 1H), 3.10 – 2.97 (m, 1H), 2.80 – 2.70 (m, 1H), 2.31 (tdd, J = 18.7, 5.1, 2.2 Hz, 2H), 1.21 (s, 1H), 0.89 (s, 9H), 0.23 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5, 138.2, 128.9, 128.7, 126.7 , 79.7, 68.4, 61.8, 55.4, 34.6, 29.5, 25.5, 17.9, -4.0, -4.2. Elemental analysis $C_{19}H_{28}O_4Si$ theoretical C 65.48% H 8.10%, experimental C 65.62% H 8.82%.

Diethyl(2*R,3*R**)-2-(((1*S**,3*S**,4*R**,6*S**)-3-benzyl-1-((tert-butyldimethylsilyl)oxy)-4,6-dihydroxy-2-oxocyclohexyl)oxy)-3-hydroxysuccinate and diethyl(2*R**,3*R**)-2-(((1*R**,3*R**,4*S**,6*R**)-3-benzyl-1-((*tert*-butyldimethylsilyl)oxy)-4,6-dihydroxy-2-oxocyclohexyl)oxy)-3-hydroxysuccinate 19**

The compound was prepared by the procedure described in article II and isolated as a mixture of inseparable isomers.

^{1}H NMR (400 MHz, $CDCl_3$): 7.37 – 7.32 (4H, m), 7.30 – 7.24 (4H, m), 7.22 – 7.15 (2H, m), 4.83 – 4.78 (1H, m), 4.69 – 4.64 (2H, m), 4.42 – 4.33 (1H, m), 4.21 – 4.14 (1H, m), 3.75 – 3.64 (2H, m), 3.52 – 3.41 (2H, m), 3.41 – 3.23 (3H, m), 3.13 – 2.91 (4H, m), 2.36 – 2.12 (4H, m), 1.85 – 1.75 (2H, m), 1.37 – 1.29 (7H, m), 1.27 – 1.16 (7H, m), 0.93 (8H, s), 0.89 (10H, s), 0.20 (3H, s), 0.18 (3H, s), 0.08 (3H, s), -0.03 (4H, s). ^{13}C NMR (101 MHz, $CDCl_3$): 203.5, 203.1, 172.1, 171.6, 171.6, 168.9, 140.1, 139.2, 130.1, 129.8, 128.6, 128.6, 126.5, 126.4, 99.7, 99.7, 72.3, 72.2, 72.0, 71.7, 71.6, 71.1, 69.1, 67.4, 62.8, 62.5, 62.4, 61.8, 56.1, 55.6, 39.7, 39.4, 32.5, 31.9, 26.1, 25.7, 19.2, 19.0, 14.3, 14.2, 14.0, -3.0, -3.1, -3.3, -3.6.

HRMS $C_{27}H_{42}O_{10}Si$ calculated $[M+H]^+$ = 555.2620, found $[M+H]^+$ = 555.2627.

(1*R,3*S**,4*R**,6*S**)-3-benzyl-1-((tert-butyldimethylsilyl)oxy)-6-hydroxy-7-oxabicyclo-[2.2.1]heptan-2-one 20**

The compound was prepared by the procedure described in article II.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.13 (m, 5H), 4.59 – 4.53 (m, 1H), 3.83 – 3.78 (m, 1H), 3.16 – 3.08 (m, 2H), 2.95 – 2.87 (m, 1H), 2.46 – 2.31 and 2.01 – 1.92 (m, 2H), 0.92 (s, 9H), 0.19 – 0.16 (m, 3H), 0.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.7, 138.1, 129.0, 128.4, 126.9, 107.6, 77.4, 69.6, 54.7, 35.0, 32.7, 25.8, 18.1, -3.6, 3.6.

HRMS $C_{19}H_{28}O_4Si$ calculated $[M+H]^+$ =349.1830, found $[M+H]^+$=349.1835

Synthesis of 4-oxo-5-phenylpentanoic acid 3f with organocatalysts.
A solution of diketone **1f** (0.1 mmol, 18.8 mg), *t*BuOOH (0.12 mmol, 21 µl) and organocatalyst (0.02 mmol) in $CDCl_3$ (0.5 mL) is stirred at room temperature. The reaction progress is monitored by ^1H NMR. After completion, the crude product is purified with column chromatography (DCM:MeOH 100:1-15:1) to afford ketoacid **3f** as a colourless oil.

Synthesis of 5-benzyl-1-methoxy-6-oxabicyclo[3.1.0]hexan-2-one 5''f with MP.
A solution of diketone **1''f** (0.1 mmol, 20.4 mg), PhIO (0.1 mmol, 11 mg) and MP (0.001 mmol) in $CDCl_3$ (0.5 mL) is stirred overnight at room temperature. The reaction progress is monitored by ^1H NMR. After completion, the crude product is purified with column chromatography (DCM:MeOH 100:1-15:1) to afford epoxide **5''f** as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): 7.39 – 7.20 (5H, m), 3.84 (3H, s), 3.12 (2H, d, J=4 Hz), 2.26 (1H, ddd, J=18, 9, 8 Hz), 2.08 – 1.94 (2H, m), 1.80 (1H, ddd, J=14, 9, 8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): 207.8, 136.0, 129.5, 128.9, 127.1, 88.1, 74.1, 56.1, 36.6, 31.8, 23.6.

HRMS $C_{13}H_{14}O_3$ calculated $[M+H]^+$=219.1016, found $[M+H]^+$=219.1017

Synthesis of 2-hydroxy-5-((5-oxo-2-phenylcyclopent-1-en-1-yl)oxy)-5-phenylcyclopent-2-en-1-one 21 with MP.
A solution of diketone **1l** (0.1 mmol, 17.4 mg), PhIO (0.1 mmol, 11 mg) and MP (0.001 mmol) in $CDCl_3$ (0.5 mL) is stirred overnight at room temperature. The reaction progress is monitored by ^1H NMR. After completion, the crude product is purified with column chromatography (Petroleum ether:EtOAc 15:1) to afford dimer **21** as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): 8.08 – 8.01 (2H, m), 7.52 – 7.40 (6H, m), 7.34 – 7.22 (2H, m), 3.53 (1H, dd, J=18.5 Hz), 3.18 (1H, dd, J=18.5 Hz), 2.99 – 2.77 (2H, m), 2.53 – 2.21 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$): 201.8, 197.8, 150.0, 149.8, 148.8, 137.5, 133.8, 130.3, 128.7, 128.6, 128.4, 128.1, 126.6, 126.0, 84.7, 38.3, 32.4, 24.2.

HRMS $C_{22}H_{18}O_4$ calculated $[M+H]^+$=347.1278, found $[M+H]^+$=347.1274

References

[1]*Modern Oxidation Methods*; Bäckvall, J.-E., Ed.; **2004**. Weinheim : WILEY-VCH.

[2]Kahlich, D.; Wiechern, K.; Lindner, J. *Ullmann's Encyclopedia of Industrial Chemistry, 5th edn., Vol. A22*, (Eds.: Elvers, B.; Hawkins, S.; Russey, W.; Schultz, G.) **1993**. Weinheim : VCH.

[3]Nijhuis, T. A.; Makkee, M.; Moulijn, J. A.; Weckhuysen, M. *Ind. Eng. Chem. Res.* **2006**, *45*, 3447-3459.

[4]Pell, M.; Korchak, E. I. (Halcon Corporation). Epoxidation using ethylbenzene hydroperoxide with alkali or adsorbent treatment recycle ethylbenzene. *U.S. Patent No. 3,439,001*, **1969**.

[5]Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

[6]Notari, B. *Catal. Today* **1993**, *18*, 163-172.

[7]Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 8310-8311.

[8]Bryliakov, K. P. *Chem. Rev*. **2017**, *117*, 11406-11459.

[9]Brown, J. W.; Nguyen, Q. T.; Otto, T.; Jarenwattananon, N. N.; Glögger, S.; Bouchard, L.-S. *Catal. Commun.* **2015**, *59*, 50-54.

[10]Que, L., Jr.; Tolman, W. B. B*. Nature* **2008**, *455*, 333-340.

[11]Amiri, N.; Le Maux, P.; Srour, H.; Nasri, H.; Simonneaux, G. *Tetrahedron* **2014**, *70*, 8836-8842.

[12]Lai, T.-S.; Zhang, R.; Cheung, K.-K.; Kwong, H.-L.; Che, C.-M. *Chem. Commun.* **1998**, 1583-1584.

[13]Howarth, J. *Tetrahedron Lett.* **2000**, *41*, 6627-6629.

[14]Fringuelli, F.; Pellegrino, R.; Piermatti, O.; Pizzo, F. *Synth. Commun.* **1994**, *24*, 2665-2673.

[15]Fatiadi, A. J. *Synthesis*, **1987**, 85-127.

[16]Muzart, J. *Chem. Rev.*, **1992**, *92*, 113-140.

[17]Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234-6458.

[18]Frauenrath, H.; Brethauer, D.; Reim, S.; Maurer, M.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 177-179.

[19]Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *J. Org. Chem.* **1994***, 59*, 4749-4759.

[20]Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637-1656.

[21]Engqvist, M.; Casas, J.; Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2053-2057.

[22]Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1997**, *38*, 5051-5057.

[23]Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. *Tetrahedron* **2002**, *58*, 7321-7326.

[24]Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges*. **1899**, *32*, 3625-3633.

[25]Ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105-4123.

[26]C. H. Hassall, *Org. React.* **1957**, *9*, 73-94.

[27]Swissman, E. E.; Bergen, J. V. *J. Org. Chem.* **1962**, *27*, 2316-2318.

[28]Gusso, A.; Baccin, C.; Pinna, F.; Strukul, G. *Organometallics* **1994**, *13*, 3442-3451.

[29]Ito, K.; Ishii, A.; Kuroda, T.; Katsuki, T. *Synlett* **2003**, *5*, 643-646.

[30]Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 6911-6914.

[31]Watanabe, A.; Uchida, T.; Ito, K.; Katsuki, T. *Tetrahedron Lett.* **2002**, *43*, 4481-4485.

[32]Murahashi, S.-I.; Imada, Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 2366-2368.

[33]Xu, S.; Wang, Z.; Zhang, Z.; Zhang, X.; Ding, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 2840-2843.
[34]Peris, G.; Miller, S. J. *Org. Lett*. **2008**, *10*, 3049-3052.
[35]Brégeault, J.-M.; Launay, F.; Atlamsani, A. *A. C. R. Acad. Sci., Ser. Ilc: Chim.* **2001**, *4*, 11-26.
[36]Ramon, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126-2208.
[37]Heravi, M. M.; Lashaki, T. B.; Poorahmad, N. *Tetrahedron: Asymmetry* **2015**, *26*, 405-495.
[38]Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240.
[39]Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603-1662.
[40]Markovič, M. *Synthesis* **2017**, *49*, 2939-2942.
[41]Sharada, A.; Rao, K. L. S.¸Yadav, J. S.; Rao, T. P.; Nagalah, K. *Synthesis* **2017**, *49*, 2483-2487.
[42]Balasubramanyam, P.; Rodríguez, A. D. *Tetrahedron* **2017**, *73*, 1283-1292.
[43]Brunel, J. M; Kagan, H.B. *Bull. Soc. Chim. France*. **1996**, 133, 1109-1115.
[44]Kanger, T.; Kriis, K.; Paju, A.; Pehk, T.; Lopp, M. *Tetrahedron: Asymmetry* **1998**, *9*, 4475-4482.
[45]Paju, A.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron Lett.* **2000**, *41*, 6883-6887.
[46] Paju, A.; Kanger, T.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2439-2448.
[47]Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1565-1573.
[48]Paju, A.; Kanger, T.; Niitsoo, O.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2393-2399.
[49]Reile, I.; Paju, A.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Tetrahedron* **2011**, *67*, 5942-5948.
[50]Paju, A.; Laos, M.; Jõgi, A.; Pari, M.; Jäälaid, R.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron Lett.,* **2006**, 4491-4493.
[51]Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958-3987.
[52]Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155-156.
[53]Curci, R.; D'Accolti, L.; Fiorentino, M. *Tetrahedron Lett.* **1995**, *36*, 5831-5834.
[54]Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491-492.
[55]Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391-1407.
[56]Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621-622.
[57]Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622-8623.
[58]Rousseau, C.; Christensen, B.; Petersen, T. E.; Bols, M. *Org. Biomol. Chem.* **2004**, *2*, 3476-3482.
[59]Lusinchi, X.; Hanquet, G. *Tetrahedron*, **1997**, *53*, 13727-13738.
[60]a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem*. **1980**, *92*, 968–969; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929– 931; b) Banfi, S.; Colonná, S.; Molinari, H.; Juliá, S.; Guixer, J. *Tetrahedron* **1984**, *40*, 5207– 5211.
[61]Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312-4348.
[62]Jense, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248-264.
[63]Fenger, T: H.; Marinescu, L. G.; Bols, M. *Eur. J. Org. Chem.* **2011**, 2339-2345.

[64]Kroutil, W., Mayon, P.; Lasterra-Sánchez, M. E.; Maddrell, S. J.; Roberts, S. M.; Thornton, S. R.; Todd, C. J.; Tüter, M. *Chem. Commun.* **1996**, 845-846.
[65]Geller, T.; Gerlach, A.; Krüger, C. M.; Militzer, H.-C. *J. Mol. Catal. A* **2006**, *251*, 71-77.
[66]Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, 1831-1834.
[67]Lygo, B.; Wainwright, P G. *Tetrahedron* **1999**, *55*, 6289-6300.
[68]Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287-1290.
[69]Lygo, B., To, D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343-1346.
[70]Xu, H.-J.; Zhu, F.-F.; Shen, Y.-Y.; Wan, X.; Feng, Y.-S. *Tetrahedron* **2012**, *68*, 4145-4151.
[71]Poudel, P. P.; Arimitsu, K.; Yamamoto, K. *Chem. Commun.* **2016**, *52*, 4163-4166.
[72]Barona-Castaño, J. C.; Carmona-Vargas, C. C.; Brocksom, T. J.; De Oliveira, K. T. *Molecules* **2016**, *21*, 310.
[73]Denisov, I. G.; Makris, T. M.; Sligar, S. G.; Schlichting, I. *Chem. Rev.* **2005**, *105*, 2253-2277.
[74]Lenoir, D. *Angew. Chem. Int. Ed.* **2006**, *45*, 3206-3210.
[75]Baglia, R. A.; Zaragoza, J. P. T.; Goldberg, D. P. *Chem. Rev.* **2017**, *117*, 13320-13352.
[76]Dolphin, D.; Traylor, T.G.; Xie, L.Y. *Acc. Chem. Res.* **1997**, 30, 251–259.
[77]Mansuy, D. *C. R. Chimie* **2007**, *10*, 392-413.
[78]Rothemund, P. *J. Am. Chem. Soc.* **1935**, *57*, 2010-2011.
[79]Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
[80] Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969-4970.
[81]Da Silva, V. S.; Nakagaki, S.; Ucoski, G. M; Idemori, Y. M.; DeFreitas-Silva, G. *RSC Adv.* **2015**, *5*, 106589-106598.
[82]Tabushi, I.; Koga, N. *J. Am. Chem. Soc.* **1979**, *101*, 6456-6458.
[83]Murahashi, S.-I.; Naota, T.; Komiya, N. *Tetrahedron Lett.* **1995**, *36*, 8059-8062.
[84]Groves, J. T.; Quinn, R. *Inorg. Chem.* **1984**, *23*, 3844-3846.
[85]Guo, C.-C.; Chu, M.-F.; Liu, Q.; Liu, Y.; Guo, D.-C.; Liu, X.-Q. *Applied Catalysis A: General* **2003**, *246*, 303-309.
[86]Fernandez-Mateos, A.; Herrero Teijon, P.; Pascual Coca, G.; Rubio Gonzalez, R.; Simmonds, M.S.J. *Tetrahedron* **2010**, *66*, 7257-7261.
[87]Gimazetdinov, A. M.; Gataullin, S. S.; Loza, V. V.; Miftakhov, M. S. *Tetrahedron* **2013**, *69*, 9540-9543.
[88]Lechuga-Eduardo, H.; Romero-Ortega, M.; Olivo, H. F. *Eur. J. Org. Chem.* **2016**, 51-54.
[89]Renaud, J.-M.; Tsoupras, G.; Stoeckli-Evans, H.; Tabacchi, R. *Helv. Chim. Acta* **1989**, *72*, 1262-1267.
[90]Takano, S.; Moriya, M.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1993**, 614-615.
[91]Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984-3988.
[92]Shimizu, H.; Okamura, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2001**, *42*, 8649-8651.
[93]Riera, A.; Moreno, M. *Molecules* **2010**, *15*, 1041-1073.
[94]Paterson, I.; Xuan, M.; Dalby, S. M. *Angew. Chem. Int. Ed.*, **2014**, *53*, 7286-7289.
[95]Mao, B.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Rev.* **2017**, *117*, 10502-10566.
[96]Frihed, T. G.; Bols, M; Pedersen, C. M. *Chem. Rev.* **2015**, *115*, 3615-3676.
[97]Winkler, J. W.; Uddin, J.; Serhan, C. N.; Petasis, N. A. *Org. Lett.* **2013**, *15*, 1424-1427.
[98]Sudhakar, G.; Bayya, S.; Kadam, V. D.; Nanubolu, J. B. *Org. Biomol. Chem.* **2014**, *12*, 5601-5610.

[99]Jõgi, A.; Ilves, M.; Paju, A.; Pehk, T.; Kailas, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2008**, *19*, 628-634.
[100]Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669-685.
[101]Nakata, K.; Kiyotsuka, Y:; Kitazume, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1345-1348.
[102]Hyodo, T.; Kiotsuka, Y.; Kobayashi, Y. *Org. Lett.,* **2009**, *11*, 1103-1106.
[103]Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851-4855
[104]Reile, I.; Paju, A.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Tetrahedron* **2011**, *67*, 5942-5948.
[105]Reetz, M. T.; Eipper, A.; Tielmann, P.; Mynott, R.; *Adv. Synth. Catal.,* **2002**, *344*, 1008-1016.
[106]Ausmees, K.; Kriis, K.; Pehk, T.; Werner, F.; Järving, I.; Lopp, M. *J. Org. Chem*, **2012**, *77*, 10680-10687
[107]Macdonald, G.; Alcaraz, L.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 5433-5436.
[108]Preegel, G.; Silm, E.; Kaabel, S.; Järving, I.; Rissanen, K.; Lopp, M. *Synthesis* **2017**, *49*, 3118-3125.
[109]Nam, W.; Jin, S. W.; Lim, M. H.; Ryu, J. Y.; Kim, C. *Inorg. Chem.* **2002**, *41*, 3642-3652.
[110]Nam, W. Oh, S.-Y.; Sun, Y. J.; Kim, J.; Kim, W.-K.; Woo, S. K.; Shin, W. *J. Org. Chem.* **2003**, *68*, 7903-7906.

Publication I

Paju, A.; Oja, K.; Matkevitš, K.; Lumi, P.; Järving, I.; Pehk, T.; Lopp, M. Asymmetric synthesis of tertiary 2-substituted 5-oxotetrahydrofuran-2-carboxylic acids. *Heterocycles* **2014**, *88*, 981-995.

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ASYMMETRIC SYNTHESIS OF TERTIARY 2-SUBSTITUTED 5-OXOTETRAHYROFURAN-2-CARBOXYLIC ACIDS

Anne Paju,[a] Karolin Oja,[a] Katharina Matkevitš,[a] Priit Lumi,[a] Ivar Järving,[a] Tõnis Pehk,[b] and Margus Lopp[a]*

[a]Department of Chemistry, Faculty of Science, Tallinn University of Technology, Akadeemia tee 15, 12618, Tallinn, Estonia; *lopp@chemnet.ee
[b]National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia

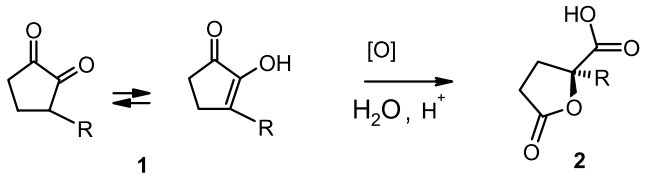
Abstract – 3-Substituted 1,2-cyclopentanediones **1** were transformed to 2-substituted 5-oxotetrahydrofuran-2-carboxylic acids **2** using a catalytic process with 0.2-0.3 equivalent of Ti(O*i*Pr)$_4$/tartaric ester/*t*BuOOH complex in up to 72% isolated yield and up to 94% *ee*. Different functional groups in the 3-alkyl substituent of **1** like, hydroxy, ether, Boc-amino and ester groups are tolerated. Boc-aminomethyl substituents lead to β-amino acid analogues and Boc-aminoethyl substituent to γ-amino acid analogues as well as spiro-lactone-lactams. A direct, two-step procedure for homocitric acid synthesis is described.

INTRODUCTION

Chiral 2-substituted 5-oxotetrahydrofuran-2-carboxylic acids are common structural units in various bioactive natural compounds like lycoperdic acid,[1] aspernolides,[2] monatins,[3] methylisocitrate,[4] sartorymensins,[5] and other compounds with potential pharmacological[6] and other applications.[3] The particular biomedicinal interest may have spiro-lactone-lactam structures.[5,6f,14]

A very simple method for diastereoselective In catalyzed synthesis of tertiary lactone structures has been described by Kumar.[7] There are several methods describing the synthesis of chiral tertiary γ-lactone structures, including enzymatic desymmetrization of parent esters for the synthesis of tertiary butenolides[8] and protein kinase C ligands.[9] In many cases chemical synthesis from natural chiral compounds is used, (e.g for the synthesis of lycoperdic acid).[10] There are a few examples of the asymmetric chemical synthesis of related structures by using the chiral auxiliaries in the synthesis of crobarbatic acid and its homologues,[11] and other chiral γ-butyrolactones.[12] Also, chiral reagents[6c] or catalysts[6g,13] have been used.

We have previously developed a method for the synthesis of enantiomerically enriched 2-alkyl-5-oxotetrahydrofuran-2-carboxylic acids **2**[15] by using the asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones **1** with a stoichiometric amount of Ti(O*i*Pr)$_4$/tartaric ester/*t*BuOOH complex[16] (Scheme 1).

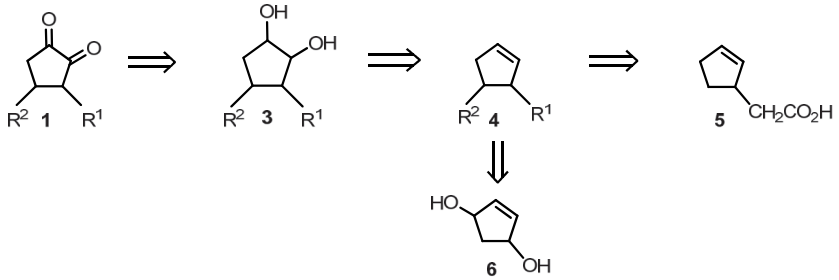


Scheme 1. General scheme for synthesis 2-alkyl-5-oxotetrahydrofuran-2-carboxylic acids **2**

Herein we describe our attempts to develop a catalytic version of the asymmetric oxidation process and broaden of the scope of the reaction by using functionalized substituents in substrate **1**, in order to obtain chiral synthons for natural compound synthesis. Using this strategy, homocitric acid lactone and spiro-lactone-lactam were synthesized.

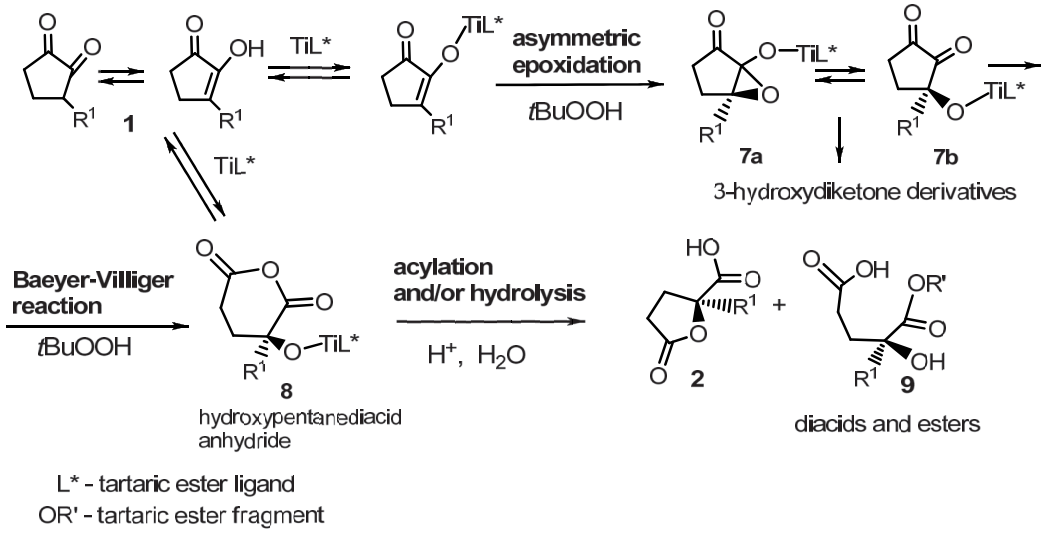
RESULTS AND DISCUSSION

The starting 3-substituted-1,2-cyclopentanediones **1** are easily accessible compounds: the preparation of compound **1a** (**a** R^1 = Bn) has been described by us earlier;[18] diketones **1b** (**b** R^1 = Me) and **1c** (**c** R^1 = Et) are commercially available. Other compounds were prepared from 3-substituted cyclopentenes by dihydroxylation, followed by Swern oxidation of the resulted diols by using our common protocols[17] (Scheme 2). In many cases the most convenient starting compound for 3-substituted cyclopentenes **4** (R^2 = H) was cyclopenten-3-acetic acid **5** (for compounds **1d-1h**; **d** R^1 = CH_2CH_2OH; **e** R^1 = CH_2CH_2OBn; **f** R^1 = CH_2NHBoc; **g** R^1 = CH_2CH_2NHBoc; **h** R^1 = CH_2CO_2tAm). Compound **1i** (R^1 = Bn, R^2 = $OSiMe_2tBu$) was prepared from commercially available *cis*-4-cyclopentene-1,3-diol **6** by mono-acylation, protection of the OH group and Grignard replacement of the acetate, followed again by a standard reaction sequence cited above.



Scheme 2. Retrosynthetic sequence for 3-substituted 1,2-cyclopentanediones **1**

We have previously shown that the oxidation of 1,2-cyclopentanediones **1** consists of three steps: epoxidation (α-hydroxylation), *in situ* Baeyer-Villiger reaction of the resulted intermediate and acylation (Scheme 3).[19] The products that may be isolated are hydroxy diketones from intermediates **7**, dioxygenated products - diacids and diacid esters **9**, and after hydrolysis and acylation lactone carboxylic acids **2**.



Scheme 3. The formal reaction cascade

Ti species participate in all steps of the cascade, catalyzing not only the oxidation but also the epoxide re-arrangement and acylation reactions. It is obvious that titanium is complexed to both, the products and the reagent. It is straightforward from Scheme 3 that a prerequisite for a catalytic reaction is the existence of equilibrium between Ti that is complexed with reaction products **8** and the substrate **1**, allowing the Ti-catalyst to enter the next catalytic cycle.

We made mixtures of the substrate **1a** (Figure 1, D) with Ti(O*i*Pr)$_4$ in CH_2Cl_2 at different substrate/Ti ratios and recorded the NMR spectra of the resulted solutions. The experimental NMR data show that Ti(O*i*Pr)$_4$ forms with substrate **1a** with a ratio of 1:2 in single clearly distinguishable complex, the spectrum of which is presented in Figure 1, A. Adding of the oxidation reagent, *t*BuOOH to the complex not only initiates the oxidation reaction, but also changes the initial complex, releasing free substrate **1a** to the reaction medium (Figure 1, B and C). These results may indicate that the complexes of Ti with *t*BuOOH and the reaction products are more stable than these with substrate **1a**.

Having this discouraging information, we made an attempt to perform the oxidation of 3-benzyl-1,2-cyclopentanedione **1a** with *t*BuOOH in the presence of various amounts of Ti(O*i*Pr)$_4$, keeping the ratio of Ti to (+)-diethyl tartrate constant in 1:1.6 . The reaction was quenched with basic

water to hydrolyze the formed esters to diacids, and then subjected to acidic treatment to lactonize the hydroxy diacids. The obtained results are presented in Table 1.

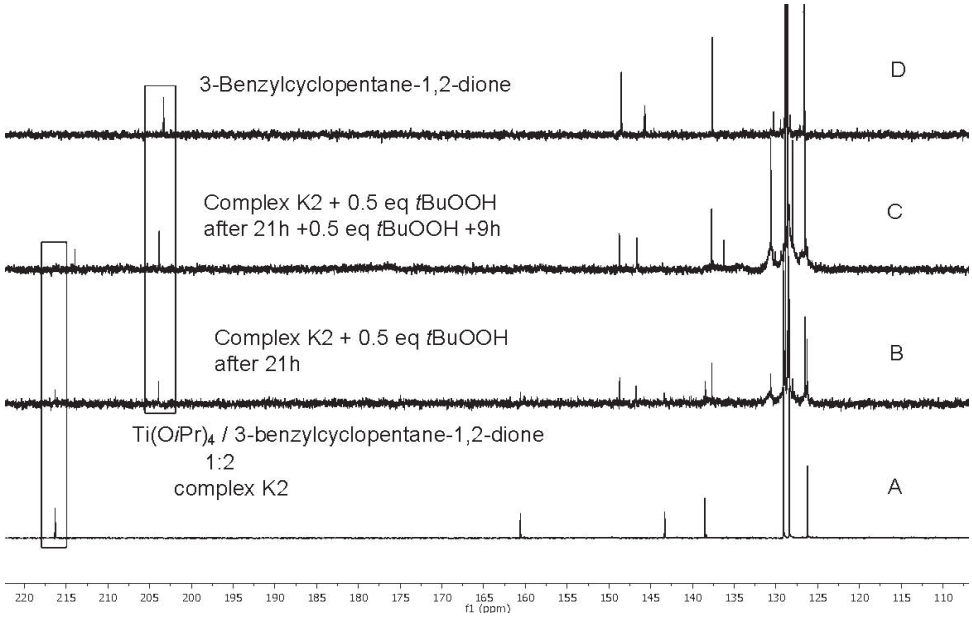


Figure 1. ^{13}C NMR spectra of the substrate **1a**, its complex with Ti(O*i*Pr)$_4$ and *t*BuOOH

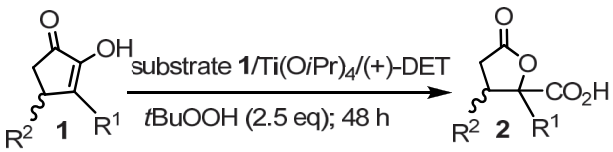
Table 1. Catalytic conditions for the oxidation of 3-benzylcyclopentane-1,2-dione **1a**

Entry	Ti(OiPr)$_4$ (eq)	(+)-DET (eq)	*t*BuOOH (eq)	Yield (%)	*ee* (%)
1	1	1.6	2.5[a]	83	96
2	0.5	0.8	2.5[a]	78	93
3	0.5	0.1	2.5[b]	42	25
4	0.3	0.48	2.5[a]	71	91
5	0.3	0.48	2.5[b]	72	93
6	0.2	0.32	2.5[b]	69	91
7	0.1	0.16	2.5[a]	26	68

[a] *t*BuOOH contains ~4% of water
[b] anhydrous *t*BuOOH was used

The data reveal that by reducing the amount of Ti (together with (+)-diethyl tartrate) to 0.5 equivalents towards substrate **1a** from the initial 1:1 amount, a slight reduction of the yield and stereoselectivity occurs (Table 1, Entries 1 and 2). Further reduction of the Ti/substrate ratio to 0.3 caused some additional reduction in the yield and stereoselectivity (Table 1, Entries 4, 5). Even at 0.2 ratio 69% yield and 91% *ee* were obtained. Also, we observed that anhydrous reaction conditions are preferable for the non-stoichiometric process, affording slightly better selectivity 91% *vrs* 93% (Table 1, Entries 4 and 5).
Reduction of the substrate Ti/**1a** ratio from 1 to 0.2 causes 5% reduction in the stereoselectivity and 14% in the yield. Keeping in mind that reduction of the catalyst fivefold may considerably simplify separation of the products, this result may be acceptable for some industrial purposes.
It is clearly seen that 0.1 eq of Ti is not sufficient for an efficient and selective process, causing already a considerable loss in the yield and stereoselectivity. Also, it is not possible to change the ratio of Ti/tartaric ester by reducing the amount of the chiral ligand because of drastic reduction in stereoselectivity and yield (Table 1, Entry 3).
We applied the found conditions (0.3 equivalents of $Ti(OiPr)_4$ and 0.48 equivalents of chiral ligand (+)-DET towards substrate) for oxidation of differently substituted substrates **1**. The formed lactone carboxylic acids were isolated and their stereoisomeric purities were determined by means of chiral HPLC. The obtained results are presented in Table 2, together with a reference of the corresponding values for a stoichiometric process.
The asymmetric oxidation method of 3-substituted 1,2-diones with Ti/tartaric ester/*t*BuOOH complex is quite universal: different functional groups like alkyl, benzyl, hydroxyl, ether, Boc-amino and ester groups are tolerated. In most cases the stoichiometric process affords the isolated yield of lactone acid ~ 70% or higher. The most remarkable feature of the process is its toleration of strong electron donating groups like Boc-aminoalkyl and ester groups. In both cases high selectivity with satisfactory yield was obtained (Table 2, Entries 8-10). The aminomethyl lactone acid **1f** has once before been detected and characterized by MS.[20] According to the best of our knowledge, aminoethyl lactone acid as well as its Boc-derivative have not been synthesized before.
The catalytic process with 0.3 Ti/substrate ratio affords slightly lower yields and selectivity than the stoichiometric process. However, in all cases the yields and the enantiomeric purities of the products are satisfactory also for the catalytic process (yield ~60% or higher and *ee* ~90%).
The racemic substrate **1i** reveals very high stereoselectivity for the oxidation of the enol double bond for both enantiomers: the resulted diastereomers had high enantiomeric purities. It means that the configuration of the protected OH group did not influence the stereoselectivity of oxidation: both enantiomers reacted with similar rate and the observed ratio of diastereomers was 1:1.

Table 2. Synthesis of substituted lactone carboxylic acids **2** from 3-substituted cyclopentane-1,2-diones **1**



a R^2 = H; R^1 = -Bn;
b R^2 = H; R^1 = -Me;
c R^2 = H; R^1 = -Et;
d R^2 = H; R^1 = -CH_2CH_2OH;
e R^2 = H; R^1 = -CH_2CH_2OBn;
f R^2 = H; R^1 = -CH_2NHBoc;
g R^2 = H; R^1 = -CH_2CH_2NHBoc;
h R^2 = H; R^1 = -CH_2CO_2tAm;
i R^2 = -$OSiMe_2tBu$; R^1 = -Bn;

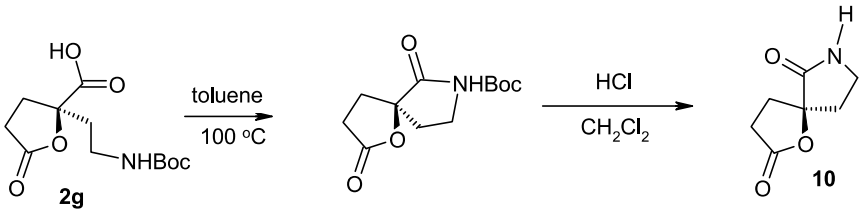
No	**1**	Lactone acid **2**			
		Yield %		*ee* %	
		Stoichiometric[a]	Catalytic[b]	Stoichiometric[a]	Catalytic[b]
1	a	83[6c]	72	96	93
2	a[c]	62[6c]	63	92	91
3	a[d]	nd	68	nd	92
4	b	75	69	94	94
5	c	72	nd	93	nd
6	d	80[e]	75[g]	95	90[g]
7	e	71[6c]	69	95	94
8	f	47	38	98	92
9	g	69	66	98	92
10	h	nd	58	nd	94
11	i	54[f]	52[f]	95/97	95/95

[a]Ratio of substrate/ $Ti(OiPr)_4$/(+) DET/ *t*BuOOH 1:1:1.6;2.5; reaction time 48 h
[b]Ratio of substrate/ $Ti(OiPr)_4$/(+) DET/ *t*BuOOH 1:0.3:0.5:2.5; reaction time 48 h
[c]Reaction time 2 h
[d]Reaction time 4 h
[e]Spirodilactone was obtained[17b]
[f]2 diastereomers at 1:1 ratio
[g] *t*BuOOH contained 4% of water

The direct cascade oxidation of 3-substituted 1,2-cyclopentanediones opens an attractive approach for the short and direct synthesis of different chiral compounds of interest. Earlier we have used a stoichiometric oxidation process for the synthesis of a natural compound homocitric acid by using hydroxyethyl-substituted diketone **1d** or acetic ester substituted diketone **1h**.[21] Now we have applied an improved protocol that enables the obtaining of homocitric acid in a two-step process using catalytical reaction conditions. Thus, diketone **1h** was subjected to asymmetric oxidation by using a standard catalytic

procedure with 0.3 equivalents of Ti(O*i*Pr)$_4$, to afford lactone acid **1h** in 58% yield and 94% *ee* (Table 2, Entry 10). After acidic hydrolysis of the *t*-amyl ester with conc. HCl, homocitric acid was obtained in 88% yield.

Lactone acids **2f** and **2g** are prospective candidates for the synthesis of analogues of β- and γ-amino acid analogues, correspondingly. We transformed lactone acid **2g** to spiro-γ-lactone-γ-lactam **10** by lactamization of **2g**, followed by removal of the Boc-group, in 59% overall yield (Scheme 4).



Scheme 4. Spiro-γ-lactone-γ-lactam **10** from lactone acid **2g**

The obtained structure may serve as a new chiral synthon for further transformations. This type of skeleton is known in many bioactive compounds.

EXPERIMENTAL

General

^{1}H and ^{13}C spectra were recorded in deuterated solvents on a Bruker AMX-500 or Avance II 400 spectrometer. Deuterated solvent peaks were used as references. 2D FT methods were used for the full assignment of ^{1}H and ^{13}C chemical shifts. Mass spectra were measured on a Shimadzu GCMS – QP 2010 spectrometer using EI (70 eV). IR spectra were recorded on a Perkin-Elmer Spectrum BX FTIR spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 Analyzer. Optical rotations were measured using a Krüss Optronic GmbH polarimeter P 3002 or Anton Paar GWB polarimeter MCP 500. High resolution mass spectra were obtained on an Accurate-Mass Q-TOF LC/MS instrument Agilent Technologies 6450 UHD by using AJ-ESI ionization. TLC was performed using DC-Alufolien Kieselgel 60 F_{254} (Merck) silica gel plates. For column chromatography silica gel KSK 40-100 μm and 100-160 μm was used. All reactions sensitive to oxygen or moisture were conducted under argon atmosphere in oven-dried glassware. Commercial reagents were generally used as received. THF was distilled from $LiAlH_4$ before use. CH_2Cl_2 was distilled from CaH_2 and stored over 3Å molecular sieve pellets. DMF and *t*AmOH was distilled from CaH_2.

(2-Cyclopent-2-enylmethyl)carbamic acid *tert*-butyl ester 4f

For the synthesis of compound **4f** one-pot Curtius rearrangement was used.[22] To a solution of cyclopent-2-enylacetic acid **5** (1.134 g, 9 mmol), NaN_3 (2.046 g, 33 mmol), TBAB (435 mg, 1.35 mmol) and zinc triflate (108 mg, 0.297 mmol) in THF (90 mL) at 45 °C di-*tert*-butyl dicarbonate (2.364 g, 9.9 mmol) was added. The reaction mixture was stirred at 45 °C for 20 h. The mixture was cooled to room temperature and 20% aqueous solution of $NaNO_2$ (75 mL) and EtOAc (80 mL) was added. After stirring for 20 min at room temperature the layers were separated and the aqueous phase was extracted with EtOAc (2x50 mL). The combined extracts were washed with saturated NH_4Cl (2x40 mL), with saturated aqueous $NaHCO_3$ (50 mL), with brine (50 mL) and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/ EtOAc 25:1 to 10:1) giving **4f** as a white solid (1.225 g, 69%); mp 46-48 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (qd, *J*=3x2.2 and 5.6 Hz, 1H, H-3), 5.62 (qd, *J*=3x2.2 and 5.6 Hz, 1H, H-2), 4.57 (bs, 1H, NH), 3.17 and 3.06 (m, 2H, H-6), 2.87 (m, 1H, H-1), 2.37 and 2.31 (m, 2H, H-4), 2.01 (tdd, *J*=2x8.8, 5.2 and 13.6 Hz, 1H, H-4), 1.51 (tdd, *J*=2x5.9, 9.2 and 13.6 Hz, 1H, H-4), 1.44 (s, 9H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.13 (C-7), 132.75 (C-2), 131.85 (C-3), 79.01 (C-8), 46.00 (C-6), 44.81 (C-1), 32.02 (C-3), 28.39 (C-9), 26.93 (C-4); IR (KBr, cm^{-1}): 3339, 3959, 2983, 2865, 1682, 1538, 1437, 1391, 1365, 1276, 1253, 1174, 1141, 1081, 989; MS (*m/z*): 198, 182, 141, 130, 124, 97, 80, 67, 57 (base); HRMS: Calcd for $C_{11}H_{19}NO_2Na$ $[M+Na]^+$ 220.1308, found 220.1317.

(2-Cyclopent-2-enylethyl)carbamic acid *tert*-butyl ester 4g

To a solution of 2-cyclopent-2-enyl-ethanol[17a] (2.24 g, 20mmol) in CH_2Cl_2 (100 mL), Et_3N (3.9 mL, 28 mmol) and methanesulfonyl chloride (1.856 mL, 24 mmol) at 0 °C were added and the mixture was stirred for 3.5 h at 0 °C. Water (200 mL) and 1N HCl solution (4 mL) were then added and the aqueous phase was extracted with CH_2Cl_2 (1x80 mL and 1x60 mL). The combined extracts were washed with brine (80 mL), dried on Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/ EtOAc 5:1) giving 3.61 g (95%) of methanesulfonic acid 2-cyclopent-2-enylethyl ester. The mixture of obtained ester (1.71 g, 9 mmol) and NaN_3 (1.024 g, 15.75 mmol) in DMF (13.5 mL) was stirred for 2 h at 50 °C and for 1.5 h at 70 °C. After cooling water (80 mL) was added and the mixture extracted with petroleum ether (80 mL), the extract was dried over Na_2SO_4. The solvent was removed under reduced pressure to yield a crude azide (1.138 g). For the conversion of azide functionality to Boc protected amine a literature procedure was used.[23] To the azide (1.138 g, 8.3 mmol) in the mixture of THF (40 mL) and water (40 mL), triphenylphosphine (4.364 g, 16.6 mmol) was added and the mixture was stirred for 2.5 h at room temperature. Then, the reaction was cooled to 0 °C, Et_3N (1.83 mL, 13.3 mmol) and di-*tert*-butyl dicarbonate (2.69 g, 12.7 mmol) were added dropwise. After stirring for 5.5 h at room temperature, water (40 mL) and Et_2O (40 mL) were added, the layers were separated and the aqueous phase was extracted with Et_2O (2x40 mL). The combined extracts were washed with brine (40 mL),

dried (Na_2SO_4) and the solvent was removed. The residue was dissolved in pentane (25 mL), the precipitate was removed by filtration and the filtrate was concentrated. Flash chromatography (silica gel, petroleum ether/acetone 100:1 to 25:1) afforded **4g** as a colorless oil (1.446 g, 76% from methanesulfonic acid 2-cyclopent-2-enylethyl ester), which physical and spectroscopic properties correspond to the data given in literature.[24]

Cyclopent-2-enylacetic acid 1,1-dimethylpropyl ester 4h

Cyclopent-2-enylacetic acid methyl ester was synthesized according to literature procedure[26] from cyclopent-2-enylacetic acid **5**. For the synthesis of compound **4h** transesterification process was used.[27] To a solution of cyclopent-2-enylacetic acid methyl ester (1.54 g, 10 mmol) in *t*AmOH (5.45 mL), Li-pieces (7 mg, 1 mmol) was added and the mixture was heated at 130 °C for 1.5 h. Then the temperature was raised to 140 °C and MeOH/*t*AmOH azeotropic mixture (1 mL) was removed. The reaction was cooled, *t*AmOH (1 mL) was added and the mixture was again heated at 130 °C for 1.5 h, followed by removal of azeotrope. This procedure was repeated four times. Finally, the volatiles were removed at 140-150 °C and the reaction mixture was cooled. Water (5 mL) was added and extracted with petroleum ether (3x6 mL), the extracts were washed with water (5 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, petroleum ether/Et_2O 60:1 to 50:1) afforded **4h** as a colourless oil (1.2 g, 61%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.73 (qd, J=3x2.2 and 5.6 Hz, 1H, H-3), 5.65 (qd, J=3x2.2 and 5.6 Hz, 1H, H-2), 3.04 (m, 1H, H-1), 2.34 and 2.28 (m, 2H, H-4), 2.29 (dd, J=6.8 and 14.7 Hz, 1H, H-6), 2.19 (dd, J=8.1 and 14.7 Hz, 1H, H-6), 2.10 (m, 1H, H-5), 1.76 (q, J=7.5 Hz, 2H, H-10), 1.45 (m, 1H, H-5), 1.41 (s, 6H, H-9), 0.87 (t, J=7.5 Hz, 3H, H-11); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.21 (C-7), 133.90 (C-2), 131.12 (C-3), 82.47 (C-8), 42.24 (C-1), 41.73 (C-6), 33.44 (C-10), 31.80 (C-4), 29.53 (C-5), 25.53 (C-9), 8.16 (C-11); IR (neat, cm^{-1}): 3053, 2975, 2852, 1730, 1462, 1368, 1265, 1145, 1061, 948, 836, 724; MS (*m/z*): 181, 167, 126, 109, 108, 79, 71, 70, 67 (base), 66, 55, 43, 41, 39.

General procedure for the synthesis of 1,2-cyclopentanediones 1f-i

(2-Cyclopent-2-enylmethyl)carbamic acid *tert*-butyl ester **4f** (2.23 g, 11.3 mmol) was dissolved in a *t*BuOH/H_2O mixture 3:1 (38 mL), fiber bound OsO_4 catalyst (7.5% OsO_4, 38 mg, 0.0113 mmol) and NMO (50 wt. % solution in water, 3.1 mL, 14.7 mmol) were added. The reaction mixture was stirred at 60 °C for 8 days (1-4 days for the other alkenes), the catalyst was filtered off, rinsed with EtOAc (3x10 mL) and aqueous solution of 10% $Na_2S_2O_3$ (40 mL) was added. The aqueous layer was extracted with EtOAc (2x50 mL and 1x30 mL), the combined extracts were washed with brine (40 mL), dried (Na_2SO_4) and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography (silica gel, petroleum ether/acetone 10:2 to 10:4) afforded 1.855 g, (71%) of the diol **3f**. The same procedure was used for diols **3g-i**. Thus, diols **3g** (2.153 g, 91%), **3h** (1.05 g, 84%) and **3i** (2.493 g, 92%) were obtained from

alkenes **4g** (2.015 g, 9.5 mmol), **4h** (1.05 g, 5.4 mmol) and **4i**[28] (2.419 g, 8.4 mmol), respectively. The diols were oxidized as followed: to a solution of DMSO (1.81 mL, 23 mmol) in CH_2Cl_2 (108 mL), TFAA (3.25 mL, 19 mmol) was added dropwise at -60 °C. The mixture was stirred for 10 min followed by the addition of the above diol (1.855 g, 8 mmol) in a DMSO/ CH_2Cl_2 mixture 1:2 (8 mL). After stirring for 1.5 h at -60 °C, Et_3N (7.4 mL, 53 mmol) was added at -60 °C and the mixture was stirred for 1.5 h at that temperature. Then the reaction mixture was warmed to ca. 5 °C, poured into a cold 1N HCl solution (220 mL) and the aqueous layer was extracted with CH_2Cl_2 (2x80 mL). The combined extracts were washed with water (200 mL), dried (Na_2SO_4) and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (80 mL), K_2CO_3 (373 mg, 2.7 mmol) was added and the mixture was stirred for 21 h at room temperature. Then, 1N HCl solution (45 mL) was added, stirred for 10 min and the aqueous layer was extracted with CH_2Cl_2 (2x40 mL). The combined extracts were washed with water (50 mL), dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, petroleum ether/ EtOAc 10:5 to 10:6) giving the target compound.

(2-Hydroxy-3-oxocyclopent-1-enylmethyl)carbamic acid *tert*-butyl ester 1f

Obtained as a white solid (1.458 g, 80%); mp 134-136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (bs, 1H, OH), 5.29 (bs, 1H, NH), 4.07 (bd J=6.0Hz, 2H, H-6), 2.47 (m, 2H, H-5, 2.42 (m, 2H, H-4), 1.43 (s, 9H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.76 (C-3), 156.54 (C-7), 149.47 (C-2), 142.99 (C-1), 80.07 (C-8), 38.71 (C-6), 31.91 (C-4), 28.23 (C-9), 23.92 (C-5); IR (KBr, cm^{-1}): 3365, 3337, 2988, 1703, 1684, 1664, 1523, 1410, 1398, 1368,1283, 1251, 1192, 1164, 1111; MS (*m/z*): 171, 154, 127, 111, 110, 84, 82, 57 (base). Anal. Calcd for $C_{11}H_{17}O_4N$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.10; H, 7.59; N, 6.15.

[2-(2-Hydroxy-3-oxocyclopent-1-enyl)ethyl]carbamic acid *tert*-butyl ester 1g

Diketone **1g** was obtained from diol **3g** (1.114 g, 4.55 mmol) as a white solid (0.722 g, 66%), which physical and spectroscopic properties correspond to the data given in literature.[25]

(2-Hydroxy-3-oxocyclopent-1-enyl)acetic acid 1,1-dimethylpropyl ester 1h

Diketone **1h** was obtained from diol **3h** (1.48 g, 6.43 mmol) as a white solid (0.766 g, 53%), mp 71-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (s, 1H, OH), 3.38 (s, 2H, CH_2CO), 2.53 (m, 2H, H-5), 2.43 (m, 2H, H-4), 1.75 (q, J=7.3Hz, 2H, CH_2CH$_3$), 1.42 (s, 6H, $(CH_3)_2$), 0.86 (t, J=7.3Hz, 3H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.16 (C-3), 168.80 (COO), 150.04 (C-2), 138.61 (C-1), 84.24 (O*C*(Me)$_2$), 35.42 (*C*H$_2$CO), 33.36 (*C*H$_2$CH$_3$), 32.01 (C-4), 25.36 (OC(*Me*)$_2$ and C-5), 8.09 (*C*H$_3$CH$_2$).; IR (KBr, cm^{-1}): 3316, 2979, 2938, 2885, 1727, 1700, 1665, 1465, 1415, 1386, 1346, 1193, 1150, 1007, 844, 696; MS (*m/z*): 226, 156, 139, 111, 71, 55, 43 (base); HRMS: Calcd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$ 249.1097, found 249.1101.

3-Benzyl-4-(*tert*-butyldimethylsilanyloxy)-2-hydroxycyclopent-2-enone 1i

Dikeone **1i** was obtained from diol **3i** (2.075 g, 6.4 mmol) as a white solid (1.532g, 75%) , mp 92-96 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.15 (m, 5H, Bn), δ 6.22 (s, 1H, OH), δ 4.67 (m, 1H, H-4), δ 3.76 (dd, J = 186.1, 14.4 Hz, 2H, Bn-CH_2), δ 2.74 and 2,27 (both dd, J = 19.5 Hz, 2H, 5-H), δ 0.90 (s, 9H, *t*Bu), δ 0.03 (s, 6H, 2 CH_3), ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.19 (C-1), 149.56 (C-2), 145.17 (C-3), 137.80 (*s*Bn), 129.13 (*o*-Bn), 128.71 (*m*-Bn), 126.66 (*p*-Bn), 66.97 (C-4), 43.35 (C-5), 31.18 (Bn-CH_2), 25.87 (*t*Bu CH_3), 18.10 (*t*Bu C), -4.30 (CH_3), -4.85 (CH_3).; IR (KBr, cm^{-1}): 3248, 3084, 1711, 1671, 1601, 1454, 1256, 1112, 1072, 835, 778, 757, 696; MS (*m/z*, %):186, 158 (base), 129, 115, 105, 91, 77, 66, 51, 41; Anal. Calcd for $C_{18}H_{26}O_3Si$: C, 67.88; H, 8.23. Found: C, 67.76; H, 8.30.

General procedure for catalytic asymmetric oxidation of 1,2-cyclopentanediones 1a-i

To a solution of Ti(O*i*Pr)$_4$ (0.18 mL, 0.6 mmol) and 4Å powdered molecular sieves (200 mg) in CH_2Cl_2 (5 mL), (+)-DET (0.164 mL, 0.48 mmol) was added at -20 °C and the mixture was stirred for 15 min. Then, cyclopentanedione (2 mmol) in CH_2Cl_2 (3.0 mL) was added and the reaction mixture was stirred for 30 min. Next *t*BuOOH (0.85 mL, 5 mmol, 5.85M solution in decane) was added and the reaction was kept at -20 °C for 48 h. Water (6.0 mL) was added and the mixture was stirred for 1 h at room temperature, then 1.8 mL of 30% aqueous NaOH in saturated aqueous NaCl solution was added and the mixture was again stirred at room temperature for an additional 1 h. The CH_2Cl_2 layer was removed and the mixture was acidified with 1M HCl solution (pH=1-2) and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (40 mL) and concentrated HCl solution (0.4 mL) was added (in the case of **2h** a catalytic amount of *p*TsOH was used as the acid and for **2f, 2g, 2i** thermal cyclization in toluene was used) and the mixture was stirred for 2 h at room temperature. Then, 20 mL of water was added and the CH_2Cl_2 layer was separated. The water layer was extracted with EtOAc and the combined extracts were dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by flash chromatography to give the corresponding γ-lactone acids **2**. Lactone acid **1a-e** correspond to the data given in literature.[15b,15c,16b]

(2*R*)-2-(*tert*-Butoxycarbonylaminomethyl)-5-oxotetrahydrofuran-2-carboxylic acid 2f

Lactone acid **2f** was obtained as a white solid (196 mg, 38%); mp 138-139 °C; $[\alpha]_D^{22}$ +9.3 (c 2.3, $CHCl_3$-MeOH 1:1); *ee* 92%; ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD): δ 3.61 and 3.56 (2d, J = 14.6 Hz, 2H, H-6), 2.64 (td, J = 2x9.7 and 18.1 Hz, 1H, H-4,), 2.54 (ddd, J = 4.0, 9.9 and 18,1 Hz, 1H, H-4), 2.36 (ddd, J = 4.0, 9.7 and 13.5 Hz, 1H, H-3), 2.27 (ddd, J = 9.7, 9.9 and 13.5 Hz, 1H, H-3), 1.38 (s, 9H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD): δ 177.07 (C-5), 172.34 (COOH), 156.85 (C-7), 86.07 (C-2), 80.28 (C-8), 44.69 (C-6), 28.29 (C-9), 28.26 (C-3), 28.21 (C-4); IR (KBr, cm^{-1}): 3386, 2984, 2939, 2613, 1797, 1785, 1748, 1656, 1537, 1464, 1392, 1290, 1260, 1185, 1161, 1098956, 922. 854, 774; HRMS: Calcd. for

$C_{11}H_{16}NO_6$ $[M\text{-}H]^-$ 258.0983, found 258.0990.

(2*R*)-2-(2-*tert*-Butoxycarbonylaminoethyl)-5-oxotetrahydrofuran-2-carboxylic acid 2g

Cyclopentanedione **1g** (237 mg, 0.98 mmol) was oxidized according to general procedure to give **2g** as a white solid (177 mg, 66%); mp 139-141 °C; $[\alpha]_D^{25}$ -14.0 (c 2.51, MeOH); *ee* 92%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (bt, J = 5.7 Hz, 1H, NH), 3.29 and 3.18 (2m, 2H, H-7), 2.70 and 1.69 (2m, 2H, H-6), 2.53 and 2.52 (2m, 2H, H-4), 2.49 and 2.15 (2m, 2H, H-3), 1.43 (s, 9H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.93 (C-5), 174.93 (COOH), 158.33 (C-8), 83.66 (C-2), 81.61 (C-9), 36.91(C-7), 36.70 (C-6), 32.99 (C-3), 27.98 (C-10), 27.72 (C-4); IR (KBr, cm^{-1}): 3406, 2982, 2591, 1784, 1526, 1370, 1254, 1174, 1197, 1029, 901, 865, 780; HRMS: Calcd. for $C_{12}H_{18}NO_6$ $[M\text{-}H]^-$ 272.1140, found 272.1142.

(2*R*)-2-(1,1-Dimethylpropoxycarbonylmethyl)-5-oxotetrahydrofuran-2-carboxylic acid 2h

Lactone acid **2h** was obtained as a white solid (301 mg, 58%); mp 38-40 °C; $[\alpha]_D^{25}$ -18.3 (c 4.74, $CHCl_3$); *ee* 94%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (br s, 1H, OH), 3.11 and 2.86 (2d, 2H, J = 16.8 Hz, CH_2CO), 2.76-2.53 (m, 3H, H-4, H-3), 2.36-2.28 (m, 1H, H-3), 1.75 (q, J = 7.5 Hz, 2H, CH_2CH_3), 1.39 (s, 6H, $(CH_3)_2$), 0.85 (t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.84 (C-5), 175.56 (COOH), 167.81 (CH_2CO), 85.33 ($OC(CH_3)_2$), 82.91 (C-2), 42.84 (CH_2CO), 33.33 (CH_2CH_3), 31.41 (C-3), 27.82 (C-4), 25.52 (CH_2CH_3), 25.50 (CH_2CH_3), 8.25 (CH_3CH_2); IR (KBr, cm^{-1}): 3445, 2981, 2945, 2886, 2595, 1786, 1730, 1464, 1388, 1371, 1187, 1152, 1069, 947, 842; HRMS: Calcd. for $C_{12}H_{17}O_6$ $[M\text{-}H]^-$ 257.1031, found 257.1040.

(2*S*,3*R*)-2-Benzyl-3-(*tert*-butyldimethylsilanyloxy)-5-oxotetrahydrofuran-2-carboxylic acid 2i and (2*S*,3*S*)-2-Benzyl-3-(*tert*-butyldimethylsilanyloxy)-5-oxotetrahydrofuran-2-carboxylic acid 2i'

Cyclopentanedione **1i** (414 mg, 1.3 mmol) was oxidized according to the general procedure to give **2i** and **2i'** as white solids in 1:1 ratio (238 mg, 52%). **2i**: mp 99-102 °C; $[\alpha]_D^{25}$ -23.5 (c 2.07, $CHCl_3$); *ee* 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.10 (m, 5H, Bn), 4.52-4.34 (m, 1H, H-3), 3.28 (dd, J = 81.6, 14.5 Hz, 2H, Bn-CH_2), 2.46 and 2.25 (2dd, J = 24.2 Hz, 2H, H-4), 0.87 (s, 9H, *t*-Bu), 0.09 (d, J = 23.5 Hz, 6H, 2 Si-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.36 (C-5), 170.51 (COOH), 133.99 (*p*-Bn), 130.54 (*m*-Bn), 128.67 (*o*-Bn), 127.49 (*s*-Bn), 91.04 (C-2), 72.44 (C-3), 40.12 (Bn-CH_2), 38.03 (C-4), 25.44 (*t*-Bu CH_3), 17.79 (*t*-Bu C), -4.74 (Si-CH_3), -5.20 (Si-CH_3). IR (KBr, cm^{-1}): 3034, 2860, 1498, 1262, 1082, 781. Anal. Calcd for $C_{18}H_{26}O_5Si$: C, 61.69; H, 7.48. Found: C, 61.65; H, 7.52.

2i': mp 110-113 °C; $[\alpha]_D^{25}$ -13.3 (c 0.72, $CHCl_3$); *ee* 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.13 (m, 5H, Bn), 4.77-4.63 (m, 1H, H-3), 3.43 – 3.08 (m, 2H, Bn-CH_2)), 2.81 and 2.39 (2dd, J = 19.1Hz, 2H, H-4), 0.96 (s, 9H), 0.20 (d, J = 15.4 Hz, 6H, 2 Si-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.13 (C-5), 171.66 (COOH), 134.73 (*p*-Bn), 130.08 (*m*-Bn), 127.83 (*o*-Bn), 126.67 (*s*-Bn), 91.58 (C-2), 72.96 (C-3), 38.44 (C-4), 37.52 (Bn-CH_2), 25.22 (*t*-Bu CH_3), 17.74 (*t*-Bu C), -5.39 (Si-CH_3), -5.50 (Si-CH_3). IR (KBr, cm^{-1}):

3483, 1770, 1705, 1497, 1254, 1085, 833, 706; HRMS: Calcd. for $C_{18}H_{27}O_5Si$ $[M+H]^+$ 351.1622, found 351.1631.

(*R*)-1-Oxa-7-azaspiro[4.4]nonane-2,6-dione 10

(2*R*)-2-(*tert*-Butoxycarbonylamino-methyl)-5-oxotetrahydrofuran-2-carboxylic acid **2g** (76 mg, 0.26 mmol) was dissolved in toluene and boiled at reflux for 9 h. After cooling, the toluene was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/acetone 10:2) giving Boc-protected spirolactam (46 mg). To the solution of obtained protected compound (46 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) concentrated HCl solution (0.1 mL) was added and the mixture was stirred for 23 hours at room temperature. Then, 6 mL of water was added and the water layer was extracted several portions with CH_2Cl_2, dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, petroleum ether/ acetone 10:5 to 10:6) gave **10** as a white solid (24 mg, 59%) from lactone acid **2g**; mp 158-160 °C; $[\alpha]_D^{22}$ +124.2 (c 2.63, $CHCl_3$); *ee* 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.26 (br s, 1H, NH), 3.53-3,47 (m, 1H, H-8), 3.39-3.33 (m, 1H, H-8), 2.97-2.88 (m, 1H, H-3) ,2.61-2.50 (m, 3H, H-3, H-4, H-9), 2.28-2.11 (m, 2H, H-9, H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.11 (C-2), 174.83 (C-6), 84.81 (C-5), 38.84 (C-8), 33.45 (C-9), 29.82 (C-4), 28.74 (C-3); IR (KBr, cm^{-1}): 3253, 2966, 1776, 1717, 1672, 1459, 1437, 1301, 1257, 1197, 1179, 1138, 1113, 1076, 1053, 1012, 982, 912, 769, 690; MS (*m/z*): 155, 137, 127, 113, 110, 100, 98, 84, 70, 56 (base), 55; HRMS: Calcd. for $C_7H_{10}NO_3$ $[M+H]^+$ 156.0655, found, 156.0651.

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REFERENCES

1. N. R-Banga, A. Welter, J. Jadot, and J. Casimir, *Phytochemistry*, 1979, **18**, 482.
2. R. R. Parvatkar, C. D'Souza, A. Tripathi, and C. G. Naik, *Phytochemistry*, 2009, **70**, 128.
3. R. Vleggaar, L. G. J. Ackerman, and P. S. Steyn, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3095.
4. S. Textor, V. F. Wendisch, A. A. DeGraaf, U. Müller, M. I. Linder, and W. Buckel, *Arch. Microbiol*., 1997, **168**, 428.
5. S. Buttachon, A. Chandrapatya, L. Manoch, A. Silva, L. Gales, C. Bruyère, R. Kiss, and A. Kijjoa, *Tetrahedron*, 2012, **68**, 3262.

6. a) P. Macheboeuf, D. S. Fischer, T. Brown, A. Zervosen, A. Luxen, B. Joris, A. Dessen, and C. J. Schofield, *Nature Chem. Biol*., 2007, **3**, 565; b) F. Wångsell, F. Russo, J. Sävmarker, Å. Rosenquist, B. Samuelsson, and M. Larhed, *Bioorg. Med. Chem. Lett*., 2009, **19**, 4711; c) O. Tamura, T. Shiro, M. Ogasawara, A. Toyao, and H. Ishibashi, *J. Org. Chem*., 2005, **70**, 4569; d) M. Witkowska, *Immun. Therap. Exper.,* 1972, **20**, 787; e) A. Pelczarska, *Arch. Immun. Therap. Exper.,* 1967, **15**, 271; f) D. L. J. Clive, D. M. Coltart, and Y. Zhou, *J. Org. Chem*., 1999, **64**, 1447; g) T. Janecki, E. Błaszczyk, K. Studzian, M. Rózalski, U. Krajewska, and A. Janecka, *J. Med. Chem*., 2002, **45**, 1142; h) J. Lee, S. Wang, G. W. A. Milne, R. Sharma, N. E. Lewin, P. M. Blumberg, and V. E. Marquez, *J. Med. Chem.,* 1996, **39**, 29.
7. P. Singh, A. Mittal, P. Kaur, and S. Kumar, *Tetrahedron,* 2006, **62**, 1063.
8. G. Pitacco, A. Sessanta, O. Santi, and E. Valentin, *Tetrahedron: Asymmetry,* 2000, **11**, 3263.
9. R. Chênevert, D. Duguay, F. Touraille, and D. Caron, *Tetrahedron: Asymmetry*, 2004, **15**, 863.
10. a) K. Makino, K. Shintani, T. Yamatake, O. Hara, K. Hatano, and Y. Hamada, *Tetrahedron,* 2002, **58**, 9737; b) H. Masaki, T. Mizozoe, T. Esumi, Y. Iwabuchi, and S. Hatakeyama, *Tetrahedron Lett*., 2000, **41**, 4801; c) J. L. Cohen and A. R. Chamberlin, *J. Org. Chem*., 2007, **72**, 9240.
11. a) T. J. Donohoe, C. A Stevenson, M. Helliwell, R. Irshad, and T. Ladduwahetty, *Tetrahedron: Asymmetry,* 1999, **10**, 1315; b) D.-P. Jang, J.-W. Chang, and B.-J. Uang, *Org. Lett.,* 2001, **3**, 983; c) M-.Y. Chen and J.-M. Fang, *J. Org. Chem*., 1992, **57**, 2937.
12. a) L. C. Dias, I. B. D. de Castro, L. J. Steil, and T. Augusto, *Tetrahedron Lett.,* 2006, **47**, 213; b) J.-M. Garnier, S. Robin, R. Guillot, and G. Rousseau, *Tetrahedron: Asymmetry*, 2007, **18**, 1434.
13. a) J-H. Kang, M. A. Siddiqui, D. M. Sigano, K. Krajewski, N. E. Lewin, Y. Pu, P. M. Blumberg, J. Lee, and V. E. Marquez, *Org. Lett*., 2004, **6**, 2413; b) A. Armstrong, C. Ashraff, H. Chung, and L. Murtagh, *Tetrahedron*, 2009, **65**, 4490.
14. S. Rana and A. Natarajan, *Org. Biomol. Chem.*, 2013, **11**, 244.
15. a) A. Paju, T. Kanger, T. Pehk, and M. Lopp, *Tetrahedron Lett.,* 2000, **41**, 6883; b) A. Paju, T. Kanger, T. Pehk, R. Lindmaa, A.-M. Müürisepp, and M. Lopp, *Tetrahedron: Asymmetry*, 2003, **14**, 1565; c) A. Paju, M. Laos, A. Jõgi, M. Päri, R. Jäälaid, T. Pehk, T. Kanger, and M. Lopp, *Tetrahedron Lett*., 2006, **47**, 4491.
16. Y. Cao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc*., 1987, **109**, 5765.
17. a) A. Paju, T. Kanger, T. Pehk, A.-M. Müürisepp, and M. Lopp, *Tetrahedron: Asymmetry,* 2002, **13**, 2439; b) A. Paju, T. Kanger, O. Niitsoo, T. Pehk, A.-M. Müürisepp, and M. Lopp. *Tetrahedron: Asymmetry*, 2003, **14**, 2393.
18. A. Jõgi, M. Ilves, A. Paju, T. Pehk, T. Kailas, A.-M. Müürisepp, and M. Lopp, *Tetrahedron:*

Asymmetry, 2008, **19**, 628.

19. I. Reile, A. Paju, A.-M. Müürisepp, T. Pehk, and M. Lopp, *Tetrahedron*, 2011, **67**, 5942.
20. E. M. Tanner and A. Miao, *Tetrahedron Lett.,* 1994, **35**, 4073.
21. a) A. Paju, T. Kanger, T. Pehk, M. Eek, and M. Lopp, *Tetrahedron,* 2004, **60**, 9081; b) M. Lopp, A. Paju, M. Eek, M. Laos, T. Pehk, and R. Jäälaid, 2007, WO2007137593 A1 20071206.
22. H. Lebel and O. Leogane, *Org. Lett.,* 2005, **7**, 4107.
23. A. Kamal, A. A. Shaik, M. Sandbhor, M. S. Malik, and S. Azeeza, *Tetrahedron: Asymmetry,* 2006, **17**, 2876.
24. M. B. Bertrand and J. P. Wolfe, *Tetrahedron,* 2005, **61**, 6447.
25. I. Reile, A. Paju, M. Eek, T. Pehk, and M. Lopp, *Synlett,* 2008, 347.
26. O. L. Chapman, K. C. Mattes, R. S. Sheridan, and J. A. Klun, *J. Am. Chem. Soc.*, 1978, **100**, 4878.
27. U. Frei and R. Kirchmayr, 1988, EP0278914 A2 19880817.
28. T. Hyodo, Y. Kiotsuka, and Y. Kobayashi, *Org. Lett*., 2009, **11**, 1103.

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Kinetic resolution of epoxy alcohols with the Sharpless Ti-isopropoxide/tartaric ester complex

Karolin Maljutenko [a], Anne Paju [a], Ivar Järving [a], Tõnis Pehk [b], Margus Lopp [a,*]

[a] Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia
[b] National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia

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ABSTRACT

When investigating the Sharpless epoxidation of enol-protected 4-hydroxy-1,2-cyclopentanediones, the ability of the asymmetric Ti(O*i*Pr)$_4$/tartaric ester complex to discriminate between enantiomeric epoxides formed in situ was discovered, leading to the epoxide opening reaction of only one enantiomer. This observation was used in the kinetic resolution of racemic substituted 2,3-epoxy-4-hydroxy-cyclopentanol, to afford enantiomerically enriched epoxyalcohols in good yields and with *ees* up to 96%.

1. Introduction

The kinetic resolution of allylic alcohols via Sharpless asymmetric epoxidation is a widely used reaction in the synthesis of various enantiomerically pure compounds[1] and in the total synthesis of several natural products.[2,3]

It has previously been found that cyclic secondary allylic alcohols are poor substrates for Sharpless kinetic resolutions.[4] In this respect, cyclohexenol has been found to be the worst compound, while substituted cyclohexenols[5] and cyclopentenols[6] afford slightly better results in the oxidations. Because of this knowledge, Sharpless asymmetric epoxidation is not usually used for the synthesis of enantiomerically pure cyclic secondary epoxy alcohols. However, there is a need for these compounds because they are important intermediates in the various regio- and stereoselective ring-opening reactions[2,7] that afford chiral building blocks and intermediates.[8]

Usually, the in situ ring opening of the epoxy alcohols formed during Sharpless kinetic resolutions is the reaction that has to be avoided,[9] thus making the synthesis of certain epoxy alcohols difficult using standard asymmetric epoxidation processes. 2-Alkyl-allylic alcohols often suffer from this limitation.[10]

Although the kinetic resolution of substituted 2,3-epoxy alcohols has been extensively studied, only a few efficient cases have been found: the resolution of *meso*-epoxy alcohols[11] (the opening of *meso*-epoxy alcohols with amines leads to chiral beta-amino alcohol units[12]) and terminal epoxy alcohols.[13]

We have previously found that the asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones with the Sharpless complex results in lactone carboxylic acids in good yield and with high *ee* values (Scheme 1, A, example a).[14] We have also reported that a hydroxyl group in the allylic or homoallylic[15,16] position plays an important role in determining the selectivity of the reaction. Thus, 3-benzyl-1,2-cyclopentanedione **5** with 4-silylprotected OH group gave lactone carboxylic acids as a mixture of two diastereomers in a 1:1 ratio with excellent enantioselectivities for both diastereomers **8** and **9** (*ee* values 97% and 95%), while the corresponding unprotected 4-hydroxy-3-benzyl-1,2-cyclopentanedione **6** afforded reduced enantiopurities of 70% *ee* and 80% *ee* for lactone acids **10** and **11**, but improved diastereoselectivity 3:1 (Scheme 1, A, example b). In the first case, only the highly stereoselective cascade oxidation[17] may occur, while in the second case the highly stereoselectivity cascade oxidation and low stereoselectivity allylic oxidation of cyclic allylic alcohol compete, reducing the enantiopurity of the resulting product.

When the enol OH in 4-hydroxy-1,2-cyclopentanedione substrate is protected, only the epoxidation of the allyl alcohol moiety may occur. The Baeyer–Villiger-type oxidation does not proceed; instead, the ring opening reaction of the resulting epoxide may occur (Scheme 1, B).[18]

Herein, the oxidation of allylic systems with the subsequent epoxide opening is investigated. First, the obtained data on the oxidation of 4-hydroxy-1,2-cyclopentanedione enol ether **1** led us to the understanding that the enantiomers of the formed epoxide behave differently in the presence of the Sharpless complex: the epoxide openings proceed at different rates. This opens up the possibility of the kinetic resolution of these epoxides. Thus,

* Corresponding author. Tel.: +372 513 6083.
E-mail address: margus.lopp@ttu.ee (M. Lopp).

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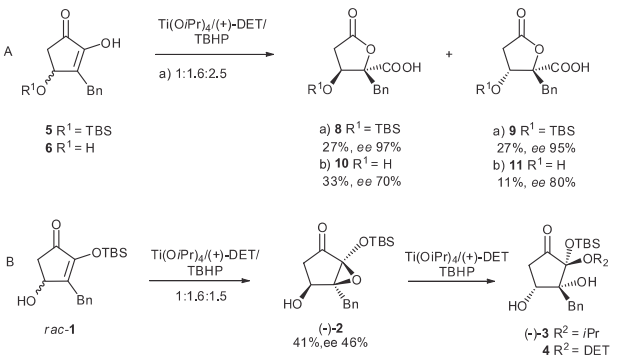


Scheme 1. Reactions of 4-hydroxy-1,2-cyclopentanediones.

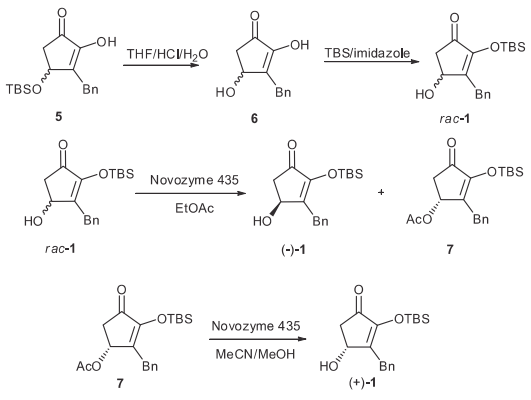
the epoxide opening of *rac*-**2**, cyclohexane epoxyalcohol *rac*-**15** and aliphatic epoxyalcohol *rac*-**13** were investigated.

Herein we have demonstrate the possibility of the kinetic resolution of racemic epoxides from 4-hydroxy-1,2-cyclopentanedione by using the Sharpless titanium isopropoxide/tartaric ester complex. We also found that with other common epoxy alcohols, the resolution is not efficient enough for preparative purposes.

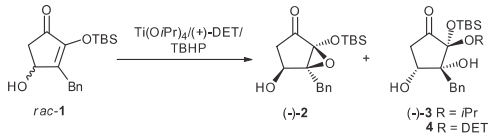
2. Results and discussion

2.1. Synthesis of substrates

The 4-silyloxy substituted 3-benzyl-1,2-cyclopentanedione **5** was prepared according to a procedure recently described by us.[14] The protecting silyl group was removed with 3 M HCl in THF to afford **6** in 70% yield. The enol hydroxyl group of **6** was selectively protected to afford *rac*-**1** (yield 66%). For the synthesis of enantiomeric alcohols, the allylic alcohol was subjected to enzymatic acylation to afford (−)-**1** (yield 60%, *ee* 88%) and enriched acetate **7** in 30% yield. The other enantiomer was obtained by enzymatic deacetalization of enriched acetate **7** with Novozyme 435, resulting in (+)-**1** (yield 79%, *ee* 99%) (see Scheme 2).



Scheme 2. Synthesis of substrates.



Scheme 3. Sharpless kinetic resolution of substrate *rac*-**1**.

2.2. Allylic oxidation of cyclopentenols

The preliminary results of the oxidation of *rac*-**1** with (+)-DET (Scheme 3) showed that the substrate with an enol-protecting silyl group reacts, as expected, as an allylic alcohol to give epoxide (−)-**2** as a single diastereomer, with modest *ee* values. Additionally, the ring opening of the resulting epoxide also occurs to a certain extent, to give isopropyl acetal **3** and tartaric ester acetal **4** (as single diastereomers) (Fig. 1). This result suggests stereodifferentiation in the epoxide opening (Table 1, No. 1).

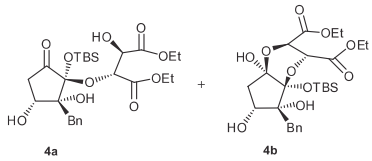


Figure 1. Tartaric ester acetals.

The epoxidation of highly enantioenriched (−)-**1** (*ee* = 96%) with Ti(O*i*Pr)$_4$/(−)-DET/TBHP complex gave epoxide (−)-**2** in 18% yield (*ee* 90%), isopropyl acetal (−)-**3** in 2% isolated yield (*ee* 98%) and DET acetal **4** in 24% isolated yield. There was 17% of unreacted substrate left, with *ee* 96%.

At the same time, the epoxidation of (−)-**1** (88% *ee*) with the Ti(O*i*Pr)$_4$/(+)-DET/TBHP complex gave epoxide (−)-**2** in 31% isolated yield and with 88% *ee*, as expected. The unreacted (−)-**1** retained its initial stereoisomeric state (88% *ee*). It is notable that in this case, no isolatable amounts of acetals **3** and/or **4** were formed.

We looked at this interesting phenomenon in more detail. When oxidizing substrates **1** with different enantiopurities with (+)-DET/TBHP complex, we observed that the product profile (ratio of acetals **3** + **4**/epoxide **2**) depended on the enantiomeric purity of the initial substrate (Fig. 2). The lower the excess of one enantiomer of the substrate, the higher the amount of formed acetals (Fig. 2).

Table 1
Sharpless epoxidation of 3-benzyl-1,2-cyclopentanedione **1**[*]

No.	DET stereoisomer	Substrate **1**	Epoxide **2**	*i*PrOH acetal **3**	DET acetals **4** (%)	Unreacted substrate **1**
1	(+)-DET	*rac*	(−)-**2**, 29%, *ee* = 46%	(−)-**3**, 7%, *ee* = 14%	21	(−)-**1**, 12%, *ee* = 16%
2	(−)-DET	(−)-**1**, *ee* = 96%	(−)-**2**, 18%, *ee* = 90%	(−)-**3**, 2%, *ee* = 98%	24	(−)-**1**, 17% *ee* = 96%
3	(+)-DET	(−)-**1**, *ee* = 88%	(−)-**2**, 31%, *ee* = 88%	—	—	(−)-**1**, 59%, *ee* = 88%

[*] Conditions: −20 °C; solvent CH_2Cl_2; overnight.

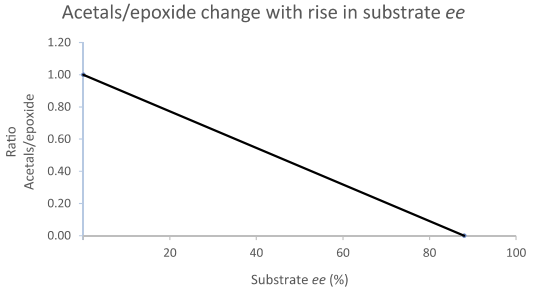
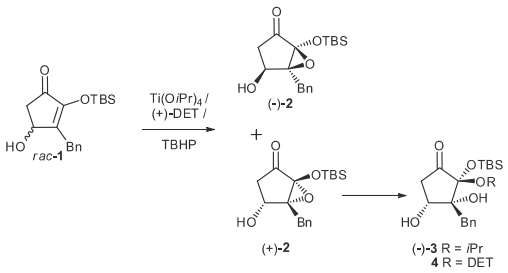


Figure 2. Illustration of the decrease in the ratio of acetals **3** + **4**/epoxide **2** with rise in substrate **1** ee value for reactions with (+)-DET (Table 1).

Figure 1 demonstrates that when the *ee* value of substrate **1** was higher, the yields of the acetals decreased. Also, in the experiment with enantiomerically enriched substrates, the combination of (−)-**1** with (−)-DET complex (Table 1, No. 2) produced more acetals than (−)-**1** with (+)-DET (Table 1, No. 3). All of the results presented above suggest a possible different behaviour of the enantiomers of the substrate and the formed epoxides with the chiral reagent. We propose that the obtained data may be rationalized as follows: in the two different reactions, epoxidation and epoxide opening, match and mismatch pairs of the substrate/reagent form, reacting at different rates and selectivities. First, the kinetic resolution in the course of the epoxidation of allylic cyclopentenol occurs with low selectivity; then, the second kinetic resolution occurs in the epoxide opening reaction (acetal formation). This reaction proceeds with high enantioselectivity and in this case the matched and mismatched pairs clearly cause different reaction rates. The (−)-**2** and (−)-DET combination results in the matched pair for epoxide opening (Table 1, No. 2). This conclusion is illustrated in Scheme 4.

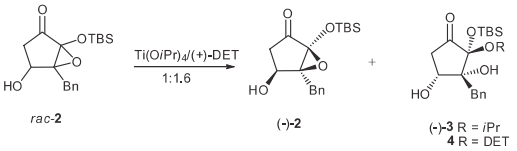


Scheme 4. Sharpless kinetic resolution of *rac*-**1** and the following epoxide opening.

If this conclusion is correct, there must be the possibility of separating the racemic 1,2-diketone epoxyalcohols by using Sharpless Ti/tartaric ester complexes.

2.3. Kinetic resolution of allylic epoxides with the Sharpless complex

Our assumption was tested by reacting racemic epoxyalcohol *rac*-**2** with the (+)-DET Sharpless complex. The selective epoxide opening should eliminate (+)-**2**. Indeed, after a 1-day reaction there was 66% of epoxide (−)-**2** left with 60% *ee* (see Scheme 5).



Scheme 5. Kinetic resolution of racemic epoxy alcohol *rac*-**2**.

The obtained DET-acetal **4** was formed in 29% and *i*PrOH-acetal **3** was formed in 4% yield (*ee* 50%). To obtained better conversion, the reaction time was prolonged to 3 days, after which 54% of highly enantioenriched unreacted epoxide (−)-**2** was left (*ee* 96%). DET-acetal **4** was formed in 36% yield and acetal **3** as a single diastereomer in 12% yield (*ee* 10%) (Table 2).

These experiments demonstrate that the kinetic resolution of epoxide *rac*-**2** in the ring opening proceeded with high selectivity. Of the formed acetals, isopropyl acetal **3** had lower enantiopurity, while tartaric ester acetal **4** gave high enantioselectivity in the epoxide opening reaction.

2.4. Kinetic resolution of other epoxy alcohols

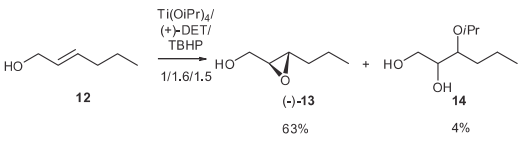
Sharpless had previously noted that after 100% conversion in the kinetic resolution of allylic alcohols, the *erythro*/*threo* ratio of the obtained epoxy alcohols increases due to an enantioselective opening process.[4] Because of this knowledge, we were further encouraged to try our conditions with other epoxyalcohols. To elucidate the scope of the reaction, attempts at the kinetic resolution of an aliphatic epoxyalcohol **13** from hex-2-en-1-ol and cyclic epoxy alcohol **15** were made. In the first case, the Sharpless oxidation led to epoxy alcohol (−)-**13** in 63% yield and with 92% *ee*. The

Table 2
Experiments with racemic epoxyalcohol **2**[*]

No.	Time (days)	DET stereoisomer	*i*PrOH acetal **3**	DET acetals **4** (%)	Unreacted substrate
1	1	(+)-DET	(−)-**3**, 4%, *ee* 50%	29	(−)-**2**, 66%, *ee* 60%
2	3	(+)-DET	(−)-**3**, 10%, *ee* 12%	37	(−)-**2**, 53%, *ee* 96%
3	4	(−)-DET	(+)-**3**, 12%, *ee* 10%	33	(+)-**2**, 55%, *ee* 93%

[*] Yields from RP-HPLC.

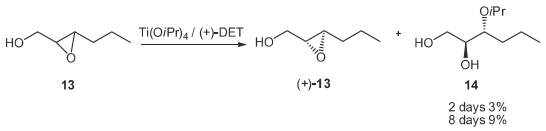
formation of a small amount of isopropyl ether **14** (4%) was also observed, which indicated that the kinetic resolution of *rac*-**12** should be possible (Scheme 6).



Scheme 6. Sharpless kinetic resolution of allylic alcohol **12**.

Compound *rac*-**13** was prepared by using an *m*CPBA oxidation of allylic alcohol **12**, resulting in 88% of the target product.

When *rac*-**13** was subjected to a reaction with the (+)-DET Sharpless complex with a substrate/reagent ratio of 1:1.6, after two days 56% of unreacted substrate (+)-**13** was left with *ee* 14% (Scheme 7). After 8 days of reaction, the enantiomeric purity of (+)-**13** increased to 42%. At the same time, several by-products formed, and we were able to isolate 9% of *i*PrOH-ether **14** (Table 3, Nos. 1–2).

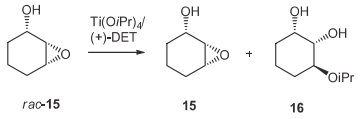


Scheme 7. Kinetic resolution of epoxy alcohol **13** with the Sharpless complex.

Table 3
Kinetic resolution of epoxy alcohols **13** and **15** with the Sharpless complex

No.	Substrate	Time (days)	Unreacted substrate	*i*PrOH-ether
1	*rac*-**13**	2	**13**; 56%, *ee* 14%	**14**; 3%
2	*rac*-**13**	8	**13**; 30%, *ee* 42%	**14**; 9%
3	*rac*-**15**	3	**15**; 44%, *ee* 6%	**16**; 1%
4	*rac*-**15**	7	**15**; 56%, *ee* 10%	**16**; 2%

We also prepared epoxyalcohol **15** from cyclohex-2-ene-1-ol with *m*CPBA in 73% yield. The kinetic resolution of the product with Ti(O*i*Pr)$_4$/(+)-DET led to a small enantioenrichment of the starting epoxide, less than in the case of the aliphatic compound **13** (Scheme 8). Prolonging the reaction time led to small improvements: after three days, **15** was isolated with 6% *ee*, and after 7 days, with 10% *ee*. We were able to isolate small amounts of *i*PrOH-ether **16** from a mixture of several by-products (Table 3, Nos. 3–4).



Scheme 8. Kinetic resolution of epoxy alcohol **15** with the Sharpless complex.

3. Conclusion

The kinetic resolution of secondary allylic cyclopentenol *rac*-**1** gives epoxides and acetals with excellent diastereoselectivity, but modest stereoselectivity. Two subsequent processes occur: allylic epoxidation, which proceeds with low stereoselectivity, and the epoxide opening, which is a highly stereoselective process. We found that the Sharpless complex is able to discriminate between enantiomeric in epoxides **2**, thus catalysing their epoxide opening at different rates. As a result, a kinetic resolution occurs, leading to acetals from predominantly one enantiomer only. The unreacted epoxide **2** can thus be obtained with high enantiomeric purity. This method is also applicable to simple racemic epoxy alcohols, such as **13** and **15**, but with less impressive results. We have demonstrated that the Sharpless complex can be used not only for epoxidation but also, as in the present case, for the kinetic resolution of racemic epoxides.

4. Experimental

The full assignment of the ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker Avance III 400 MHz or Bruker Avance III 800 MHz instrument. High resolution mass spectra were recorded by using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Elemental analyses were done by using Elementar vario Micro. IR spectra were recorded on a Bruker Tensor 27 FT infrared spectrophotometer. MS spectra were measured on a Shimadzu GSMS-QP2010 spectrometer on a 70 eV EI. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. Chiral GC was performed using Shimadzu GC-2010 Supelco β-DEX™ 225 column (30 m × 0.25 mm). Chiral HPLC was performed using Chiralpak AD-H (250 × 4.6 mm), Chiralcel OJ-H (250 × 4.6 mm), Chiralcel OD-H (250 × 4.6 mm), Chiralpak AS-H (250 × 4.6 mm) or Lux 3u Amylose-2 (250 × 4.6 mm) columns. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel Kieselgel 40–63 μm was used. Purchased chemicals and solvents were used as received. DCM was distilled over phosphorous pentoxide. Petroleum ether has a boiling point 40–60 °C. The reactions were performed under air atmosphere without additional moisture elimination unless stated otherwise.

4.1. Synthesis of 3-benzyl-2,4-dihydroxycyclopent-2-enone 6

To a solution of diketone **5** (1.017 g, 3.2 mmol) in THF (20 mL), a 3 M HCl solution (7.7 mL) was added, and the reaction mixture was stirred for 3 h at room temperature. Next, H_2O (40 mL) was added and the mixture was extracted 3 times with EtOAc. The extracts were dried over $MgSO_4$, and the crude product was purified by column chromatography (heptane:acetone 10:3). 394 mg (60%) of diketone **6** were obtained as a colourless oil. **6**: ^{1}H NMR (400 MHz, MeOD) δ 7.37–7.07 (m, 5H, Ph), 4.53 (d, J = 6.1 Hz, 1H, H-4), 3.94 and 3.54 (2d, J = 14.2 Hz, 2H, Ph-CH_2), 2.74–2.62 (m, 1H, H-5), 2.21–2.10 (m, 1H, H-5). ^{13}C NMR (101 MHz, MeOD) δ 201.10 (C-1), 149.88 (C-2), 145.42 (C-3), 137.87 (*s*-Ph), 129.10 (Ph), 128.66 (Ph), 126.54 (*p*-Ph), 65.96 (C-4), 42.68 (C-5), 31.16 (Ph-CH_2). IR (film, cm^{-1}): 3265, 1702, 1658, 1385, 1049, 980, 762, 637. MS (*m*/*z* %): 186, 158, 129 (main peak), 115, 105, 91, 77, 65, 51. Elemental analysis calcd for $C_{12}H_{12}O_3$ C, 70.57; H, 5.92; found C, 69.76; H, 6.19.

4.2. Synthesis of 3-benzyl-2[*tert*-butyldimethylsilyl]oxy-4-hydroxycyclopent-2-enone *rac*-1

Diketone **6** (110 mg, 0.54 mmol) was dissolved in CH_2Cl_2 (5 mL), after which imidazole (52 mg, 0.77 mmol) and TBSCl (89 mg, 0.59 mmol) were added. The mixture was stirred at room temperature for 1.5 h, after which H_2O (10 mL) was added. The mixture

was extracted 3 times with CH_2Cl_2, and the extracts were dried over $MgSO_4$. The obtained crude product was purified by column chromatography (heptane:EtOAc 20:1–20:3). 269 mg (66%) of diketone *rac*-**1** was obtained as a colourless oil. *rac*-**1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H, Ph), 4.60 (d, J = 5.5 Hz, 1H, H-4), 3.94 and 3.61 (2d, J = 14.4 Hz, 2H, Ph-CH_2), 2.73–2.63 (m, 1H, H-5), 2.26–2.18 (m, 1H, H-5), 1.92 (br s, 1H, OH), 0.98 (s, 9H, *t*-Bu), 0.26 and 0.25 (s, 6H, CH_3-Si-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.95 (C=O), 150.83 (C-2), 150.28 (C-3), 137.77 (*s*-Ph), 129.09 (Ph), 128.94 (Ph), 126.84 (*p*-Ph), 66.25 (C-4), 42.89 (C-5), 31.65 (Ph-CH_2), 25.86 (*t*-Bu CH_3), 18.52 (*t*-Bu C), −3.71 (Si-CH_3), −3.90 (Si-CH_3). IR (film, cm^{-1}): 3252, 2856, 1748, 1496, 1389, 1258, 1064, 837, 779, 701. Elemental analysis calcd for $C_{17}H_{26}O_3Si$ C, 67.88; H, 8.23; found C, 67.38; H, 8.36.

4.3. Synthesis of (4*S*)-3-benzyl-2[*tert*-butyldimethylsilyl]oxy-4-hydroxycyclopent-2-enone (−)-1

Novozym SP 435 (195 mg) was added to a solution of diketone **1** (195 mg, 0.61 mmol) in EtOAc (4 mL). The reaction mixture was then stirred overnight after which it was filtered and concentrated. The products were separated by column chromatography (Heptane:EtOAc 10:1). Product (−)-**1** (151 mg, 77%) was obtained as a colourless oil and acylated diketone **7** (39 mg, 18%) was obtained as a colourless oil. (−)-**1**: $[\alpha]_D^{25}$ = −89.6 (*c* 1.27, $CHCl_3$); IR (film, cm^{-1}): 3421, 3064, 1720, 1642, 1365, 1253, 1117, 1053, 840, 699; HPLC: AD-H Hex–*i*PrOH 97:3, 1 ml/min, 210 nm, ee = 88%, major 9.1 min, minor 11.9 min.

4.4. Synthesis of (4*R*)-3-benzyl-2[*tert*-butyldimethylsilyl]oxy-4-dihydroxycyclopent-2-enone (+)-1

Novozym SP 435 enzyme (225 mg) was added to a solution of acylated diketone **7** (150 mg, 0.42 mmol) in MeCN/MeOH (7.5 mL, 0.3 mL of MeOH and 7.2 mL of MeCN). After 4 days the reaction mixture was filtered and concentrated. The crude product was purified by column chromatography (Heptane:EtOAc 10:1). Diketone (+)-**1** (104 mg, 79%) was obtained as a colourless oil. (+)-**1**: $[\alpha]_D^{25}$ = +122.8 (*c* 0.36, $CHCl_3$); HPLC: AD-H Hex–*i*PrOH 97:3, 1 ml/min, 210 nm, ee = 99%, major 11.9 min, minor 8.9 min.

4.5. Synthesis of 1-benzyl-5-[*tert*-butyldimethylsilyl]oxy-2-hydroxy-6-oxabicyclo[3.1.0]hexane-4-one (+)-2

At first, (−)-DET (0.14 mL, 0.78 mmol) was added at −20 °C under an argon atmosphere to a solution of Ti(O-*i*-Pr)$_4$ (0.15 mL, 0.49 mmol) and molecular sieves (49 mg) in CH_2Cl_2 (3 mL). After 15 min of stirring, compound **1** (156 mg, 0.49 mmol) was added as a solution in CH_2Cl_2 (1 mL). After stirring for 30 min, TBHP (0.13 mL, 0.78 mmol) was added. After an overnight reaction, diethyl ether (10 mL) and a saturated Na_2SO_4 solution (0.49 mL) were added at −20 °C and the mixture was stirred for 2 h at room temperature. The mixture was filtered through Celite and concentrated. The crude mixture was purified by column chromatography (Heptane:EtOAc 15:1–10:3) to afford 60 mg (37%) of epoxide (+)-**2** as an amorphous solid, 19 mg (10%) of acetal (+)-**3** as a colourless oil and 49 mg (18%) of acetals **4** as a colourless oil. (+)-**2**: $[\alpha]_D^{25}$ = +72.7 (*c* 1.7, $CHCl_3$), ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.43–7.11 (m, 5H, Ph), 4.10 (d, J = 6.0 Hz, 1H, H-2), 3.44 and 3.04 (2d, J = 14.2 Hz, 2H, Ph-CH_2), 2.55–2.04 (m, 2H, H-3), 0.99 (s, 9H, *t*-Bu), 0.34 (s, 3H, Si-CH_3), 0.24 (s, 3H, Si-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.67 (C=O), 135.55 (*s*-Ph), 129.62 (Ph), 129.09 (Ph), 127.35 (*p*-Ph), 88.27 (C-5), 73.81 (C-1), 65.43 (C-2), 41.33 (C-3), 33.23 (Ph-CH_2), 25.71 (*t*-Bu CH_3), 18.14 (*t*-Bu C), −3.84 (Si-CH_3), −4.03 (Si-CH_3). IR (KBr, cm^{-1}): 3000, 1764, 1608, 1496, 1254, 1065, 858, 702. HPLC: AS-H Hex–*i*PrOH 97.5:2.5, 1 ml/min, 210.8 nm, ee = 58%, major 9.7 min, minor 8.4 min. HRMS (ES) m/z calcd for $[M-H]^-$ 333.1528; found 333.1524.

4.5.1. 3-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-3,4-dihydroxy-2-isopropoxycyclopentanone (+)-3

$[\alpha]_D^{25}$ = +127 (*c* 0.07, $CHCl_3$) ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32–7.17 (m, 5H, Ph), 4.44–4.34 (m, 1H, H-4), 4.03 (hept, J = 6.2 Hz, 1H, *i*Pr CH), 3.06 and 2.97 (2d, J = 13.8 Hz, 2H, Ph-CH_2), 2.69 (dd, J = 19.4, 8.7 Hz, 1H, H-5), 2.48 (s, 1H, 3-OH), 1.98 (dd, J = 19.4, 7.4 Hz, 1H, H-5), 1.21 (s, 1H, 4-OH) 1.16 and 0.92 (2d, J = 6.2 Hz, 6H, *i*Pr 2 × CH_3), 0.79 (s, 9H, *t*-Bu), 0.20 (s, 3H, Si-CH_3), −0.00 (s, 3H, Si-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.24 (C=O), 137.32 (*s*-Ph), 130.39 (Ph), 129.06 (Ph), 127.07 (*p*-Ph), 101.88 (C-2), 78.97 (C-3), 69.95 (C-4), 65.61 (*i*Pr CH), 40.45 (C-5), 37.15 (Ph-CH_2), 26.03 (*t*-Bu CH_3), 24.89 (*i*Pr CH_3), 23.16 (*i*Pr CH_3), 18.81 (*t*-Bu C), −2.94 (Si-CH_3), −3.32 (Si-CH_3). HPLC: AD-H Hex:*i*PrOH 97:3, 1 ml/min, 210 nm, ee = 74%, major 4.9 min, minor 5.9 min. HRMS (ES) m/z calcd for $[M-H]^-$ 393.2103; found 393.2116.

4.5.2. 3-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-2,3,4-trihydroxycyclopentane-1-one diethyl tartrate acetal 4a

^{1}H NMR (800 MHz, chloroform-*d*) δ 7.33–7.28 (m, 5H, Ph), 4.75 (d, J = 3.6 Hz, 1H, DET CHO), 4.45 (br dd, J = 8.0, 3.6 Hz, 1H, DET C*H*OH), 4.34–4.22 (m, 4H, DET OCH_2), 4.23 (br s, 1H, 4-OH), 4.18–4,15 (br m, 1H, H-4), 3.76 (s, 1H, 3-OH), 3.35 (d, J = 8.9 Hz, 1H, DET OH), 3.17 (d, J = 14.2 Hz 1H, Ph-C*H*$_2$), 2.67 (dd, J = 20.0, 7.9 Hz, 1H, H-5), 2.52 (d, J = 14.2 Hz, 1H, Ph-C*H*$_2$), 2.36 (dd, J = 20.0, 4.2 Hz, 1H, H-5), 1.34 and 1.32 (2t, J = 7.2 Hz, 6H, DET C*H*$_3$), 0.93 (s, 9H, *t*-Bu), 0.41 (s, 3H, Si-CH_3), 0.09 (s, 3H, Si-CH_3). ^{13}C NMR (201 MHz, chloroform-*d*) δ 208.44 (C=O), 171.28 (DET C=O), 169.65 (DET C=O), 136.22 (*s*-Ph), 130.68 (*o*-Ph), 128.62 (*m*-Ph), 127.08 (*p*-Ph), 102.26 (C-2), 79.24 (C-3), 74.17 (DET CHO), 72.44 (DET CHO), 68.50 (C-4), 62.36 (DET OCH_2), 62.02 (DET OCH_2), 41.34 (C-5), 38.07 (Ph-CH_2), 25.89 (*t*-Bu CH_3) 18.70 (*t*-Bu C), 14.22 (DET CH_3), 14.11 (DET CH_3), −2.60 (Si-CH_3), −4.13 (Si-CH_3). HRMS (ES) m/z calcd for $[M+Na]^+$ 563.2283; found 563.2298.

4.5.3. 3-Benzyl-2-((*tert*-butyldimethylsilyl)oxy)-2,3,4-trihydroxycyclopentane-1-one diethyl tartrate diacetal 4b

^{1}H NMR (800 MHz, chloroform-*d*) δ 7.29–7.24 (m, 5H, Ph), 4.55 (d, J = 9.3 Hz, 1H, DET CHO), 4.47 (d, J = 9.3 Hz, 1H, DET CHO), 4.27–4.22 (m, 2H, DET OCH_2), 4.12 and 4.11 (2q, J = 7.2 Hz, 2H, DET OCH_2) 3.77 (s, 1H, 3-OH) 3.74 (br m, 1H, H-4), 3.15 (br s, 1H, 1-OH), 3.06 (d, J = 14.7 Hz, 1H, Ph-CH_2), 2.90 (dm, J = 14.7 Hz, 1H, Ph-CH_2), 2.85 (br d, J = 10.4 Hz, 1H, 4-OH), 2.55 (dd, J = 16.5, 7.9 Hz, 1H, H-5), 2.26 (dm, J = 16.5 Hz, 1H, H-5), 1.30 and 1.29 (2t, J = 7.2 Hz, 6H, DET C*H*$_3$), 1.00 (s, 9H, *t*-Bu), 0.47 (s, 3H, Si-CH_3), 0.29 (s, 3H, Si-CH_3). ^{13}C NMR (201 MHz, chloroform-*d*) δ 167.67 (DET C=O), 167.15 (DET C=O), 136.49 (*s*-Ph), 131.12 (*o*-Ph), 128.17 (*m*-Ph), 126.73 (*p*-Ph), 100.24 (C-2), 99.34 (C-1), 80.49 (C-3), 72.57 (DET CHO), 69.41 (C-4), 69.11 (DET CHO), 62.38 (DET OCH_2), 62.23 (DET OCH_2), 40.46 (C-5), 37.93 (Ph-CH_2), 26.24 (*t*-Bu CH_3), 18.75 (*t*-Bu C), 14.08 (DET CH_3), 14.02 (DET CH_3), −1.56 (Si-CH_3), −3.11 (Si-CH_3).

4.6. General procedure for the synthesis of racemic epoxy alcohols

To a solution of allylic alcohol (1 mmol) in CH_2Cl_2 (3.5 mL), *m*-CPBA (1.2 equiv) was added at 0 °C. The mixture was allowed to gradually warm up to room temperature. After 30 min, 1.5 mL of saturated $NaHCO_3$ and 1.5 ml of 10% $Na_2S_2O_3$ were added and the mixture was stirred for 30 min. The organic layer was separated and the mixture was extracted with CH_2Cl_2, then washed with saturated $NaHCO_3$ and brine, and dried with Na_2SO_4. The

filtered and concentrated crude product was purified by column chromatography (Petroleum ether:Acetone 10:2).

4.7. Procedure for the kinetic resolution of *rac*-2, *rac*-13 and *rac*-15

At first, (−)-DET (0.16 mL, 0.82 mmol) solution in CH_2Cl_2 (0.5 mL) was added at −20 °C under an argon atmosphere to a solution of Ti(O*i*Pr)$_4$ (0.16 mL, 0.51 mmol) and molecular sieves (51 mg) in CH_2Cl_2 (2.5 mL). After 15 min of stirring, the epoxyalcohol substrate (0.55 mmol) was added as a solution in CH_2Cl_2 (2 mL). After an overnight reaction, diethyl ether (11 mL) and saturated Na_2SO_4 solution (0.51 mL) were added at −20 °C and the mixture was stirred for 2 h at room temperature. The mixture was then filtered through Celite and concentrated. The crude mixture was purified by column chromatography with Hept:EtOAc 15:1–10:3 mixture to yield 89 mg (53%) of epoxide (−)-**2**, 6 mg (4%) of acetal **3** and 43 mg (16%) of acetals **4**.

4.8. Kinetic resolution of 2,3-epoxyhexanol 13

From the epoxyalcohol substrate **13** (87 mg, 0.75 mmol) with (−)-DET (0.23 mL, 1.2 mmol), Ti(O*i*Pr)$_4$ (0.23 mL, 0.75 mmol) in CH_2Cl_2 (7 mL), 49 mg (56%) of epoxyalcohol (+)-**13** and 4 mg (3%) of isopropyl ether **14** were obtained. The data for the compounds were in accordance with the literature.[19] **13** $[\alpha]_D^{25}$ = +1.7 (*c* 0.49, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94–3.86 (m, 1H), 3.66–3.57 (m, 1H), 2.98–2.89 (m, 2H), 2.02–1.87 (m, 1H), 1.59–1.40 (m, 4H), 0.95 (t, J = 7.3 Hz, 3H). Chiral GC β-DEX™ 225 column: *ee* = 14% major 11.0 min, minor 10.8 min. 3-Isopropoxyhexane-1,2-diol **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83–3.75 (m, 1H), 3.75–3.68 (m, 1H), 3.65–3.58 (m, 2H), 3.51 (dt, J = 7.0, 3.9 Hz, 1H), 2.71 (br, 2H), 1.60–1.26 (m, 4H), 1.15 and 1.14 (2d, J = 6.1 Hz, 2 × 3H), 0.93 (t, J = 7.0 Hz, 3H).

4.9. Kinetic resolution of 2,3-epoxycyclohexanol 15

From the epoxyalcohol substrate **15** (69 mg, 0.7 mmol), (−)-DET (0.21 mL, 1.12 mmol), Ti(O*i*Pr)$_4$ (0.2 mL, 0.7 mmol) in CH_2Cl_2 (6.5 mL), 35 mg (44%) of epoxyalcohol **15** were obtained. The data for the epoxyalcohol were in accordance with the literature.[20] HPLC analysis was performed after benzoylation of the product. **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04–3.95 (m, 1H), 3.36–3.28 (m, 2H), 2.20–2.11 (m, 1H), 1.91–1.68 (m, 2H), 1.61–1.49 (m, 2H), 1.50–1.37 (m, 1H), 1.32–1.18 (m, 1H). HPLC AD-H 95:5, 1 ml/min, 230 nm, major 7.9 min, minor 9.1 min, *ee* = 10%.

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References

1. Shibuya, H.; Kawashima, K.; Narita, N.; Ikeda, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1992**, *40*, 1154–1165.
2. Li, X.; Jiao, X.; Liu, X.; Tian, C.; Dong, L.; Yao, Y.; Xie, P. *Tetrahedron Lett.* **2014**, *55*, 6324–6327.
3. Rodriguez-López, J.; Ortega, N.; Martin, V. S.; Martin, T. *Chem. Commun.* **2014**, 3685–3688.
4. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.
5. Yamamoto, H.; Oritani, T. *Biosci., Biotechnol., Biochem.* **1994**, *58*, 992–993.
6. Take, K.; Okumura, K.; Tsubaki, K.; Taniguchi, K.; Shiokawa, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1903–1907.
7. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560–1563.
8. Krishna, P. R.; Nomula, R.; Krishna, V. S. R. *Tetrahedron Lett.* **2014**, *55*, 3381–3383.
9. Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 5413–5415.
10. Lu, L. D.-L.; Johnson, A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 731–733.
11. Belonok, Y. N.; Chusov, D.; Peregudov, A. S.; Yashkina, L. V.; Timofeeva, G. I.; Maleev, V. I.; North, M.; Kagan, H. B. *Adv. Synth. Catal.* **2009**, *351*, 3157–3167.
12. Kumar, M.; Kureshy, R. I.; Ghosh, D.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C. *ChemCatChem* **2013**, *5*, 2336–2342.
13. Luo, L.; Yamamoto, H. *Org. Biomol. Chem.* **2015**, *13*, 10466–10470.
14. Paju, A.; Oja, K.; Matkevitš, K.; Lumi, P.; Järving, I.; Pehk, T.; Lopp, M. *Heterocycles* **2014**, *88*, 981–995.
15. Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1565–1573.
16. Paju, A.; Kanger, T.; Niitsoo, O.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2393–2399.
17. Paju, A.; Kanger, T.; Pehk, T.; Lopp, M. *Tetrahedron Lett.* **2000**, *41*, 6883–6887.
18. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560–1563.
19. Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 1222–1225.
20. Elhalem, E.; Comin, M. J.; Rodriguez, J. B. *Eur. J. Org. Chem.* **2006**, 4473–4482.

Publication III

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Aerobic cascade oxidation of substituted cyclopentane-1,2-diones using metalloporphyrin catalysts

Karolin Maljutenko, Victor Borovkov, Dzmitry Kananovich, Ivar Järving, Margus Lopp*

Tallinn University of Technology, Department of Chemistry and Biotechnology, Akadeemia tee 15, Tallinn 12618, Estonia

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Aerobic oxidation

ABSTRACT

A method for the aerobic cascade oxidation of cyclopentane-1,2-diones using metal porphyrins as catalysts, yielding hydroxydiacids **2**, ketoacid **3** and diketoacids **4** which are the intermediates of important biologically active compounds is reported. This method is operationally simple and can be employed under ambient conditions.

1. Introduction

Currently, the development of sustainable chemical processes is one of the major challenges in chemical engineering and applied science. Over the past decades, various transition metal catalysts have been successfully utilized in combination with different oxidizing reagents, such as peroxides, hydroperoxides, peracids and others, to convert alkenes to epoxides or carbonyl compounds.[1–3] However, from both economic and ecological points of view, the use of atmospheric oxygen as a terminal oxidant is more attractive due to its high natural abundance (nearly 20% of air is oxygen) and environmental sustainability. The main limitation for wide application of atmospheric oxygen in oxidation reactions is its relatively low reactivity in ambient conditions and lack of selectivity. Therefore, the selection of a catalyst is vital to carry out aerobic oxidations of different substrates in an efficient manner. Among known catalysts for performing aerobic oxidations of organic compounds,[4,5] synthetic metalloporphyrins, mimics of the oxygen carrier and oxidation catalyst in living organisms, are remarkably efficient and prospective.[6,7] In contrast to natural enzymatic systems, the selectivity of artificial catalysts is governed by the careful choice of a transition metal ion and by modifications in the skeleton of the porphyrin catalyst.[6]

Metalloporphyrin-catalyzed air oxidation has so far been used sparsely in organic syntheses to oxidize various compounds and functional groups. For example, it has been used in the oxidation of alkanes,[7–13] alkenes,[7,11,14–16] aromatic hydrocarbons,[7,17,18] steroids,[19,20] and aldehydes.[11,32] The listed examples represent only oxidation reactions, without considering subsequent transformations. However, in the preparation of pharmaceuticals or complex biologically active compounds, as a rule, a multi-step synthesis is necessary. Therefore, the development of catalytic conditions to assist reaction cascades is of importance.

In the present paper we report the first example of a cascade air oxidation of reactive organic molecules. Substituted cyclopentane-1,2-diones (**1**, Scheme 1) have been chosen as substrates because of their multiple functional groups sensitive to oxidation, allowing the formation of oxidation cascades which result in producing hydroxydiacid **2**. Also, the other oxidation products[21–23] of these structures have demonstrated interesting biological activities (e.g. clionamides[22] and dichotomain B.[23]). Hydroxydiacids **2** have also been used as precursors for the synthesis of nucleoside analogues[24] and HIV-1 protease inhibitors.[25] On the other hand, ketoacid **3** is also a viable substrate for the synthesis of γ-lactones,[26] whilst diketoacid **4** is a valuable precursor for the synthesis of heterocycles, including bioactive compounds.[27] Moreover, hydroxydiacid **2** contains an asymmetric center, which may open up additional opportunities for the elaboration of an enantioselective oxidation approach using chiral porphyrin catalysts.[28,29]

We found that enol derivatives **1** can be easily oxidized by air, using a catalytic amount of metalloporphyrin catalyst (1–5 mol%), affording 2-substituted-2-hydroxydiacids **2**, and other ring-cleaved

* Corresponding author.
E-mail address: lopp@chemnet.ee (M. Lopp).

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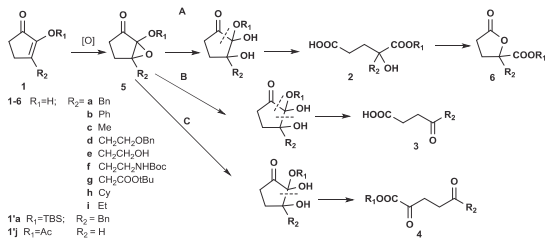

Scheme 1. Reaction oxidative cascade of **1.**

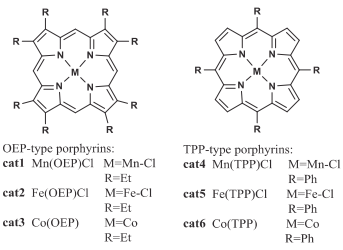

Fig. 1. Used TPP- and OEP-type metalloporphyrin metal complexes.

compounds, such as ketoacids **3** and diketoacids **4**. On the basis of our earlier studies,[30,31] we can suggest a following cascade of occurring aerobic oxidation reactions (Scheme 1): in all cases the first reaction is the epoxidation of the enol double bond (formation of intermediate **5**). The second oxidation reaction that may depend on the oxidizing reagent is a Baeyer-Villiger reaction leading to hydroxydiacid **2** (which easily converse to lactone acid **6**, route A), or the combination of a Bayer-Villiger reaction and diol cleavage resulting in ketoacid **3** (route B), or only a diol cleavage reaction yielding the diketoacid **4** product (route C). The reactions proceed under mild conditions, at ambient temperature and normal air pressure, and the method is operationally simple (see supplementary info).

2. Results and discussion

For initial catalyst screening, conventional 3-benzylsubstituted ketoenol (**1a**) was a selected as a substrate. The most frequently used transition metal complexes (Mn, Fe, and Co) of octaethylporphyrin (OEP) and tetraphenylporphyrin (TPP) were used as catalysts (Table 1 and Fig. 1).

The oxidation of **1a** without presence of catalyst proceeds, as expected, considerably slower (81% of unreacted substrate), without any selectivity (Table 1, No. 1). In reactions with the catalysts, it was found that formation of different products **2a**, **3a** or **4a** was highly dependent on the central metal ion of the porphyrin complex. In the case of the Mn complexes **cat1** and **cat4** (Table 1, No. 2, 5 and 6) mostly diacid **2a** and ketoacid **3a** were formed, while diketoacid **4a** was not observed (route A and route B). However, with Co (**cat3** and **cat6**) and with Fe porphyrin complexes (**cat2** and **cat5**) the reaction yielded mostly diketoacid **4a** and ketoacid **3a** (route C and double oxidation according to route B; Table 1, No. 3, 4, 7 and 8). The yield of hydroxydiacid **2a** was up to 55% in the best case with Mn catalyst (Table 1, No. 6), for ketoacid **3a** the highest yield was 67% (Table 1, No. 2) and for **4a** 48% (Table 1, No. 8).

Table 1
Oxidation of 3-benzyl-cyclopentane-1,2-dione **1** (enol form) with air using different porphyrin metal complexes as a catalyst.

No	Catalyst	Loading mol%	Unreacted 1a,%	Products,%		
				2a	3a	4a
1	-	–	81	10	9	–
2	**cat1**	5	–	33	67	–
3	**cat2**	5	30	–	30	40
4	**cat3**	5	49	–	18	33
5	**cat4**	5	–	54	46	–
6	**cat4**	1	3	55	42	–
7	**cat5**	5	31	–	37	32
8	**cat6**	5	20	8	24	48

Reaction conditions: $CDCl_3$; rt; 5 mol% catalyst; 24 h. Product composition determined by ^1H NMR.

The substrate was completely consumed in the case of Mn catalysts (**cat1** and **cat4**; Table 1, No. 2 and 5). However, it the case of Fe catalysts (**cat2** and **cat5**) and with Co catalysts **cat3** and **cat6**, a certain amount of substrate remained unreacted (from 20 to 49%; Table 1, No. 3, 4, 7 and 8). From Mn catalysts Mn (TPP)Cl **cat4** was more efficient, affording a considerably higher yield of the target product hydroxyl diacid **2a** than **cat1**; (55% vs 33%; Table 1, No. 2 and 6). It was also found that **cat4** was efficient even with 1 mol% of catalyst (Table 1, No. 6). However, with preliminary results Mn catalysts had poor chemoselectivity: pathways A and B formed an almost equimolecular mixture of compounds **2** and **3** (55%–42% in the best case). To follow the formation of **2a** and **3a**, the kinetics of these compounds were monitored by ^1H NMR. The obtained curves clearly indicate that hydroxydiacid **2a** and ketoacid **3a** form in parallel reactions (Fig. 2).

An effort was made to affect the relative rates of these reactions by using different solvents and **cat4** because of its highest selectivity towards formation of diacid **2**. The results are presented in Table 2.

With the initial chlorinated solvents both transformations were fast but not selective (Table 2, No. 1 and 2). Benzene did not give any improvement in selectivity (Table 2, No. 3). From the investigated solvents the best selectivity for **2** was obtained by using toluene, with a 75/16 ratio of **2a** to **3a** (Table 2, No. 4). The selectivity was very sensitive to temperature-both lowering and increasing of temperature decreased the selectivity towards **2** (Table 2, No. 4–8).

The use of ether solvent (THF) and alcohol (MeOH) completely hindered the reaction (Table 2, No. 9 and 10, respectively), while in dimethylcarbonate (DMC) only the formation of 31% of ketoacid **3** was observed (Table 2, No. 11).

Previously it has been shown that external ligands are able to accelerate porphyrin-catalyzed oxidation reactions.[33,34] However, in our case the addition of pyridine (10 mol%) or a basic and widely used organocatalyst, squaramide[35] (10 mol%), to the porphyrin

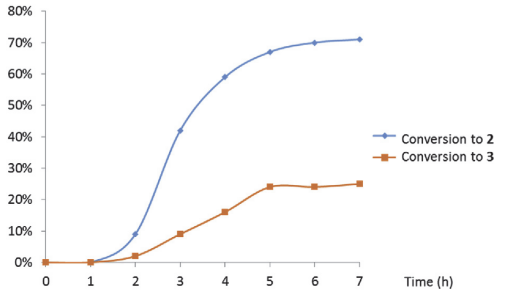

Fig. 2. Reaction monitoring results.

Table 2
Solvent and temperature screening with **1a**.

No	Solvent	Temp °C	Time [h]	Additive 10 mol%	Unreacted 1a%	2a,%	3a,%
1	$CDCl_3$	rt	2	–	3	55	42
2	CH_2Cl_2	rt	2	–	–	54	46
3	Benzene	rt	24	–	–	56	44
4	Toluene	rt	18	–	9	75 (63[a])	16 (16[a])
5	Toluene	5 °C	18	–	11	28	61
6	Toluene	15 °C	18	–	9	61	30
7	Toluene	30 °C	18	–	3	38	59
8	Toluene	40 °C	2	–	6	35	59
9	THF	rt	24	–	100	–	–
10	MeOH	rt	24	–	100	–	–
11	DMC	rt	2	–	69	–	31
12	Toluene	rt	24	pyridine	100	–	–
13	Toluene	rt	24	squaramide	100	–	–
14	Toluene	rt	24	imidazole	12	35	53
15	Toluene	rt	24	BHT	100	–	–
16	Toluene	rt	24	TEMPO[b]	100	–	–

Catalyst **cat4**; 1 mol%. The composition of the reaction mixtures was determined by ^{1}H NMR.
[a] Isolated yield.
[b] 1 equivalent.

complex **cat4** (1 mol%) had a negative impact on the catalytic reaction and no transformation was observed during 24 h at rt (Table 2, No. 12 and 13). Another coordination agent, methyl imidazole (10 mol%) redirected the reaction towards the formation of ketoacid **3a** (53%) while the conversion to **2a** was 35% (Table 2, No. 14).

In general, there are several possible mechanisms for metalloporphyrin-catalyzed oxidations, including a radical pathway.[36] Since there are no additional agents, such as oxygen-carriers or reductants in our particular cases, a radical mechanism is the most plausible. In order to support this assumption, the **cat4** mediated reaction was performed in the presence of radical scavengers. It was found that both BHT (10 mol%) and TEMPO (1 eq) blocked the reaction completely (Table 2, No. 15 and 16). This finding supports the radical character of the reaction according to pathway A (see references[37,38]) as a new example of radical Baeyer-Villiger oxidation. The reactivity of other substrates towards oxidation also corroborates our assumption (Table 3).

To elucidate the scope of the reaction, the oxidation of differently substituted enols of cyclopentane-1,2-diones **1** was carried out by using **cat4** as a porphyrin complex. The results are presented in Table 3. First it was found that enols with protected OH are unreactive: the free hydroxyl group is necessary for the oxidation. Thus, substrates **1'a** and **1'j** did not give any products after 24 h (Table 3, No. 2, 11), which means that the hydroxyl group deprotonation may be the initial step of the reaction. The phenyl group as a substituent at the enol double bond inhibits the reaction. The effect of this substituent on the electron density of the double bond has been studied before.[39,40] In the case of porphyrin catalysts phenyl substituted substrate **1b** is inert in the oxidation (Table 3, No. 3). At the same time methyl-substituted diketone **1c** afforded tertiary oxidized products in 34% total yield (**2c** in 11% yield, and its *in situ* lactonized derivative **6c** in 23% yield). However, the double oxidation occurred predominantly, affording ketoacid **3c** in 66% yield, after a 24 h reaction (Table 3, No. 4). These results show that the difference in the substituent-dependent electron density on the double bond of substrates and steric hindrance that prevents the formation of catalytic complexes are both important factors for the oxidation reaction catalyzed by porphyrins. Indeed, the substrates with electron withdrawing groups and bulky substituents, such as phenyl **1b**, CH_2CH_2NHBoc **1f** and $CH_2COOtBu$ **1g**, make the double-bond too electron-deficient for the reaction to occur or produce the excessive bulkiness which inhibits the oxidation (Table 3, No. 3,7 and 8) whilst with electron-donating and less sterically hindered groups, such as benzyl **1a**, methyl **1c**, CH_2CH_2OBn **1d**, CH_2CH_2OH **1e**, Cy **1h** and ethyl **1i**, the oxidation proceeded more readily (Table 3, No. 1, 4, 5, 6 and 10).

Interestingly, while with most reactive substrates the reaction resulted in diacids **2** and ketoacids **3**, substrate **1h** with bulky Cy group as substituent selectively produced only diketoacid **4h**.

Table 3
Oxidation of substituted substrates **1** with air oxygen in the presence of porphyrin catalyst **cat4**.

No	Substrate	Time	Conversion to 2a-d	Conversion to 3/4
1	**1a**	18 h	75% (63%[a])	16% (16%[a]) **3a**
2	**1'a**	24 h	–	–
3	**1b**	24 h	–	–
4	**1c**	24 h	11% (and **6c** 23%)	66% **3c**
5	**1d**	48 h	51%[a]	43%[a] **3d**
6	**1e**	48 h	33%[a]	–
7	**1f**	48 h	–	–
8	**1g**	48 h	–	–
9	**1h**	48 h	–	86% **4h**
10	**1i**	48 h	40%[a]	16%[a] **3i**
11	**1'j**	24 h	–	–

Catalyst **cat4** (Mn (TPP)Cl); 1 mol%. The composition of the reaction mixtures was determined by ^{1}H NMR.
[a] Isolated yield.

3. Conclusion

The possibility to use environmentally friendly metal complexes of porphyrin for a cascade aerobic oxidation of substituted cyclopentane-1,2-diones was demonstrated. The reactions proceed with moderate to good chemoselectivity to afford the corresponding oxidation products hydroxy diacids **2**, ketoacids **3** and diketoacids **4**. The use of manganese metalloporphyrins affords diacids **2** with up to 75% yield. This method is operationally simple, environmentally benign, does not require the use of harmful oxidants and reductants, and can be used under ambient conditions. Further studies to increase the selectivity, to understand the detail mechanism, and to widen the applicability of this synthetic approach are in progress and will be reported in due course.

4. Experimental section

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a 400 MHz or 500 MHz instrument. Residual solvent signals were used as internal standards. High resolution mass spectra were recorded by using an Q-TOF LC/MS spectrometer by using ESI ionization. IR spectra were recorded on a Bruker Tensor 27 FT infrared spectrophotometer. Mass spectra were measured on a Shimadzu GCMS – QP 2010 spectrometer using EI (70 eV). Precoated silica gel 60 F254 plates were used for TLC. Column chromatography was performed on a preparative purification system with silica gel Kieselgel 40–63 μm. Purchased chemicals and solvents were used as received. Petroleum ether has a boiling point of 40–60 °C. The reactions were performed under air atmosphere. The porphyrins used for the reactions were commercially obtained from PorphyChem.

4.1. Synthesis of diacid **2**

A solution of diketone **1a** (18.8 mg, 0.1 mmol) and Mn (TPP)Cl (0.7 mg, 0.001 mmol) in toluene (0.5 mL) is stirred overnight (18 h) at room temperature. The reaction progress is monitored by ^{1}H NMR. After completion, the crude product is purified with column chromatography (CH_2Cl_2:MeOH 100:1–15:1) to afford diacid **2a** (15 mg, 63% isolated yield) and ketoacid **3a** (3 mg, 16% isolated yield) as colourless oils.

4.2. Synthesis of diketoacid **4**

A solution of diketone **1** (18.8 mg, 0.1 mmol) and Fe (TPP)Cl (0.7 mg, 0.001 mmol) in THF (0.5 mL) is stirred overnight (18 h) at room temperature. The reaction progress is monitored by ^{1}H NMR. After completion, the crude product is purified with column chromatography (CH_2Cl_2:MeOH 100:1–15:1) to afford ketoacid **3a** (12 mg, 60% yield) and diketoacid **4a** (3 mg, 20% yield) as unisolable mixture.

2,5-Dioxo-6-phenylhexanoic acid 4a: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39–7.17 (m, Bn, 5H), 3.75 (s, CH_2-Bn, 2H), 3.14–3.06 (m, H-3, 2H), 2.95–2.87 (m, H-4, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0 (C-5), 194.4 (C-2), 159.3 (C-1), 133.6 (s-Bn), 129.4 (o or m-Bn), 128.9 (o or m-Bn), 127.3 (p-Bn), 49.6 (C-6), 36.0 (C-4), 31.2 (C-3). HRMS (ESI) calculated for $C_{12}H_{12}O_4$, $[M-H]^-$: 219.0663, found 219.0675. MS (*m/z*): 220, 202, 175, 129, 101, 91, 73, 65, 55. The compound was obtained as a yellow oil.

4.3. Synthesis of 3-cyclohexyl-2-hydroxycyclopent-2-en-1-one **1h**

A 2N HCl solution (0.43 mL) is added to a solution of 2-((tert-butyldimethylsilyl)oxy)-3-cyclohexylcyclopent-2-en-1-one (52 mg, 0.18 mmol) in THF (1 mL). After 5 days, 2 mL of water is added to the reaction mixture and extracted 3× with DCM. The combined organic phase are washed with brine and dried through a phase separator. After column chromatography (Petroleum ether:EtOAc 10:1), compound **1h** is obtained as a yellow oil in 70% yield (25 mg, 0.14 mmol). ^{1}H NMR (400 MHz, Chloroform-d) δ 6.02–5.83 (m, 1H), 2.67 (ddd, $J = 11.5, 8.0, 3.5$ Hz, 1H), 2.42 (d, $J = 5.0$ Hz, 2H), 2.40–2.36 (m, 2H), 1.84–1.67 (m, 5H), 1.46–1.28 (m, 5H), 1.28–1.15 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6, 152.3, 147.6, 147.6, 38.1, 31.8, 30.2, 26.2, 26.1, 22.8. HRMS (ESI) calculated for $C_{11}H_{16}O_2$, $[M+H]^+$: 181.1223, found 181.1215.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.12.009.

References

1. Paju A, Oja K, Matkevitš K, et al. *Heterocycles*. 2014;88:981.
2. Chen S, Lui Z, Chen L, et al. *Org Lett*. 2011;13:2274.
3. Che C-M, Huang J-S. *Chem Commun*. 2009:3996.
4. Punniyamurthy T, Velusamy S, Iqbal J. *Chem Rev*. 2005;105:2329.
5. Ghogare AA, Greer A. *Chem Rev*. 2016;116:9994.
6. Meunier B. *Chem Rev*. 1992;92:1411.
7. Jiang G, Liu Q, Guo C. *Biomimetic Based Applications*vol. 2. China: Prof. M. Cavrak, InTech; 2011:32–58.
8. Guo C-C, Liu X-Q, Li Y, Chu M-F, Zhang X-B. *J Mol Catal Chem*. 2003;192:289.
9. Zhou W, Hu B, Sun C, Xu S, Liu Z. *Catal Lett*. 2011;141:1709.
10. Xu S, Hu B, Cui Q, Hu T, Huang X, Liu Z. *Adv Mater Res*. 2011;233–235:1093–1096.
11. Jiang G, Chen J, Thu H-Y, Huang J-S, Zhu N, Che C-M. *Angew Chem Int Ed*. 2008;47:6638.
12. Guo C-C, Liu X-Q, Liu Q, Liu Y, Chu M-F, Lin W-Y. *J Porphyr Phthalocyanines*. 2009;13:1250.
13. Yang W-Y, Tao N-Y, Guo C-C. *J. Cent. South Univ. Technol*. 2007;14:660.
14. Yan Y, Kang E-H, Yang K-E, et al. *Catal Commun*. 2004;5:387.
15. Li XD, Zhu YC, Yang LJ. *Chin Chem Lett*. 2012;23:375.
16. Kalajahi SSM, Hajimohammadi M, Safari N. *Reac Kinet Mech Cat*. 2014;113:629.
17. Sun C, Hu B, Liu Z. *Chem Eng J*. 2013;232:96.
18. Huang G, Yuan RX, Peng Y, et al. *RSC Adv*. 2016;6:48571.
19. Borovkov VV, Solovieva AB, Cheremenskaya OV, Belkina NV. *J Mol Catal Chem*. 1997;120:L1.
20. Solovieva AB, Borovkov VV, Lukashova EA, Grinenko GS. *Chem Lett*. 1995:441.
21. Ballatore C, Gay B, Huang L, et al. *Bioorg Med Chem Lett*. 2014;24:4171.
22. Hao X, Wu J, Tian H, Shi Y, Lin J, Tian W. *Chin J Chem*. 2015;33:1235.
23. Shao L-D, Wu Y-N, Xu J, et al. *Nat Prod Bioprospect*. 2014;4:181.
24. Jõgi A, Paju A, Pehk T, Kailas T, Müürisepp A-M, Lopp M. *Tetrahedron*. 2009;65:2959.
25. Joshi A, Veron J-B, Unge J, et al. *Med Chem*. 2013;56:8999.
26. Sakai N, Horikawa S, Ogiwara Y. *RSC Adv*. 2016;6:81763.
27. Ju Y, Miao D, Yu R, Koo S. *Org Biomol Chem*. 2015;13:2588.
28. Carminati DM, Intrieri D, Caselli A, et al. *Chem Eur J*. 2016;22:13599.
29. Simonneaux G, Tagliatesta P. *J Porphyr Phthalocyanines*. 2004;8:1166.
30. Reile I, Paju A, Müürisepp A-M, Pehk T, Lopp M. *Tetrahedron*. 2011;67:5942.
31. Paju A, Kanger T, Lindmaa R, Müürisepp A-M, Lopp M. *Tetrahedron: Asymmetry*. 2003;14:1565.
32. Wang X, She Y. *Front Chem Eng China*. 2009;3:453.
33. Renaud J-P, Battioni P, Bartoli JF, Mansuy D. *J Chem Soc Chem Commun*. 1985:888.
34. Srour H, Jalkh J, Le Maux P, Chevance S, Kobeissi M, Simonneaux G. *J Mol Catal Chem*. 2013;370:75.
35. Rouf A, Tanyeli C. *Curr Org Chem*. 2016;20:2996.
36. Evans S, Smith JRL. *J Chem Soc Perkin Trans*. 2000;2:1541.
37. Cavani F, Raabova K, Bigi F, Quarantelli C. *Chem Eur J*. 2010;16:12962.
38. Robertson JC, Swelim A. *Tetrahedron Lett*. 1967;30:2871.
39. Jõgi A, Paju A, Pehk T, et al. *Synthesis*. 2006;18:3031.
40. Paju A, Laos M, Jõgi A, et al. *Tetrahedron Lett*. 2006;47:4491.

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Lühikokkuvõte

Asendatud tsüklopentaan-1,2-dioonide oksüdeerimine

Asendatud tsüklopentaan-1,2-dioonid on reaktiivsed orgaanilised molekulid, millega saab teostada palju erinevaid keemilisi reaktsioone. Reaktsiooni kulg sõltub tavaliselt reagendist ja substraadi struktuurist, keto-enoolsest tasakaalust jne. Erinevate oksüdeerijatega oksüdeerimisreaktsioonides võivad need ühendid oksüdeeruda erineval viisil ja määral. See tähendab, et asendatud tsüklopentaan-1,2-dioone saab epoksüdeerida, hüdroksüleerida ja oksüdatiivselt lõhustada (Baeyer-Villigeri reaktsiooniga, 1,2-dioolide lõhustamisega jne), et saada soovitud produkte. Kuna need oksüdeerimisreaktsioonide produktid võivad olla mitmete oluliste ühendite sünteesiks kasulikud vaheühendid, on nende kemo- ja stereoselektiivsete oksüdeerimismeetodite väljatöötamine väärtuslik ja oluline.

Uurimaks asendatud 1,2-tsüklopentaandioonide asümmeetrilist oksüdeerimist ja leidmaks tingimusi erinevate sünteetiliselt oluliste oksüdatsiooniproduktide selektiivseks moodustumiseks, kasutati titaan-katalüütilist ja metalloporfüriinidel põhinevat oksüdatsiooni.

Esmalt kirjeldati meetodit, mis kasutab Ti-tetraisopropoksiidi/viinhappe estri/*t*BuOOH kompleksi (Sharplessi katalüsaatorit) mittestöhhiomeetrilises koguses, et sünteesida kõrge enantioselektiivsusega dikarboksüülhappeid (mida saab muundada laktoonkarboksüülhapeteks). Sharplessi kompleksi kasutati ka 4-hüdroksüülasendatud 3-bensüültsüklopentaan-1,2-diooni oksüdeerimiseks, mille tulemusena saadi tsüklilisi epoksüalkohole ja teisi oksüdeerimisprodukte. Arendati välja meetod tsükliliste epoksüalkoholide kineetiliseks lahutamiseks, kasutades Ti-tetraisopropoksiidi/tartraadi estri ja *t*BuOOH kompleksi, mis annab enantiomeerselt rikastatud sünteetiliselt väärtuslikke epoksüalkohole. Selgitati välja võimalikud reaktsiooni toimumise ja produktide moodustumise viisid.

Laiendamaks 3-asendatud tsüklopentaan-1,2-dioonide oksüdeerimiseks kasutatavate katalüsaatorite hulka, uuriti erinevaid organokatalüsaatoreid ja metalloporfüriine. Tulemused näitasid, et katalüsaatorid olid üldiselt mitteselektiivsed. Samas, ühe kiraalse metalloporfüriiniga saavutatud väike enantiomeerne liig viitas, et selle lähenemisega võib saavutada stereoselektiivsust ning antud ala edasiuurimine erinevate porfüriinide struktuuri seisukohast on mõttekas.

Abstract

Oxidation of substituted cyclopentane-1,2-diones

Substituted cyclopentane-1,2-diones are reactive organic molecules which undergo many chemical reactions. The reaction pathway usually depends on the reagent and the substrate structure: the nature of the substituent, keto-enol equilibrium *etc*. In oxidation reactions with different oxidants, these compounds may be oxidised in different ways and to different extents. This means that substituted cyclopentane-1,2-diones can also be epoxidised, hydroxylated and oxidatively cleaved in different ways (*via a* Baeyer-Villiger reaction, 1,2-diol cleavage *etc*.), yielding a variety of products. Since the products of these oxidation reactions can be useful intermediates for the synthesis of many compounds, the development of chemo- and stereoselective methods of oxidation is of great value and importance.

To investigate the asymmetric oxidation of substituted 1,2-cyclopentanediones and find conditions for the selective formation of different synthetically useful oxidation products, Ti-catalysed and metalloporphyrin-based oxidation reactions were used.

First, a method was described which involves using a non-stoichiometric amount of a Ti-tetraisopropoxide/tartaric ester/*t*BuOOH complex (the Sharpless catalyst) for the synthesis of different dicarboxylic acids (transforming to lactone carboxylic acids) with high enantioselectivity. The complex was also used to oxidise 4-hydroxyl-substituted 3-benzyl-cyclopentane-1,2-dione resulting in synthetically valuable cyclic epoxyalcohols. The possible reaction pathways and product formation were rationalised.

Furthermore, a method for the kinetic resolution of cyclic epoxyalcohols by using a Ti-tetraisopropoxide/tartaric ester/*t*BuOOH complex resulting in enantiomerically enriched epoxyalcohols and their opening products was developed.

To broaden the scope of oxidation catalysts for the oxidation of 3-substituted cyclopentane-1,2-diones, organocatalysts and metalloporphyrins were used, and the obtained results showed that the catalysts were mainly non-selective. However, a small enantiomeric excess obtained with one chiral metalloporphyrin indicates the possibility of stereoselection with that approach and provides motivation for further research in the area.

Curriculum vitae

Personal data

Name: Karolin Oja (Maljutenko)
Date of birth: 22.08.1988
Place of birth: Estonia
Citizenship: Estonian

Contact data

E-mail: karolin.oja@ttu.ee

Education

2013– 2018 Tallinn University of Technology—PhD
2011– 2013 MSC, Tallinn University of Technology
2008– 2011 BSC, Tallinn University of Technology
2004– 2007 High school, Tallinn English College

Language competence

Estonian	Native speaker
English	Fluent
Russian	Beginner

Professional employment

2013–2016 – TUT, Department of Chemistry, engineer
2016–2017 – TUT, Department of Chemistry, junior researcher
2017–… –TUT, Department of Chemistry and Biotechnology, junior researcher

Supervised theses

2014–2016 Anni Larin BSc thesis, defended in TUT

Awards

2014–Tiina Mõis doctoral Scholarship

Elulookirjeldus

Isikuandmed

Nimi: Karolin Oja (Maljutenko)
Sünniaeg: 22.08.1988
Sünnikoht: Eesti
Kodakondsus: Eesti

Kontaktandmed

E-post: karolin.oja@ttu.ee

Hariduskäik

2013–2018 Tallinna Tehnikaülikool – PhD
2011–2013 MSC, Tallinna Tehnikaülikool
2008–2011 BSC, Tallinna Tehnikaülikool
2004–2007 Keskharidus, Tallinna Inglise Kolledž

Keelteoskus

Eesti keel	emakeel
Inglise keel	kõrgtase
Vene keel	algtase

Teenistuskäik

2013–2016 – TTÜ, keemiainstituut, insener
2016–2017 – TTÜ, keemiainstituut, nooremteadur
2017–… –TTÜ, keemia ja biotehnoloogia instituut, nooremteadur

Juhendatud lõputööd

2014–2016 Anni Larin bakalaureusetöö, kaitstud TTÜ-s

Tunnustused

2014–Tiina Mõisa doktoriõppe stipendium