α-Hydroxylation of β-Dicarbonyl Compounds

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Abstract: The most convenient and direct route to α-hydroxy-β-dicarbonyl compounds is the oxidation of readily accessible 1,3-dicarbonyls. Hence, this type of oxidation is an intensively investigated field. In this short review, we present and compare α-hydroxylations using various oxidants such as peracids (Rubottom oxidation), dimethyldioxirane or molecular oxygen. From an economical and ecological point of view, metal-catalyzed air oxidations are optimal at least for cyclic β-dicarbonyls. For asymmetric α-hydroxylations only chiral sulfonyloxaziridines are available to date. Thus, there is still a need for significant development in this area.

Keywords: atom economy; carbonyl compounds; oxidation; oxygen; reagents; synthetic methods

1 Introduction

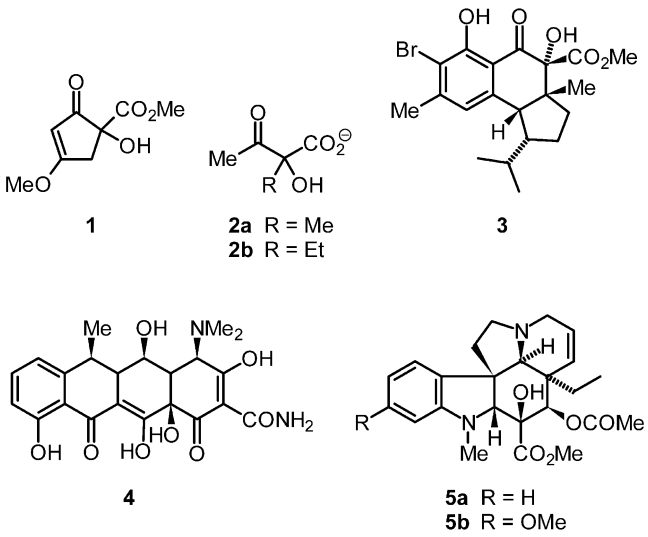
The α-hydroxy-β-dicarbonyl moiety is a common structural motif in a variety of natural products and pharmaceuticals. Among these are antibiotics such as kjellmanianone (**1**),[1] hamigeran A (**3**)[2] or doxycycline (**4**),[3] shown in Scheme 1. α-Acetolactate (**2a**) and α-acetohydroxybutyrate (**2b**)[4] are the biosynthetic precursors of valine and isoleucine (Scheme 1). Moreover, this functional unit appears in key intermediates in many multi-step reaction sequences, for example, in the synthesis of the *Aspidosperma* alkaloids 11-demethoxyvindoline (**5a**) and vindoline (**5b**).[5]

The most convenient synthetic route to α-hydroxylated products is the direct oxidation of 1,3-dicarbonyl compounds **6**, which are readily accessible by numerous procedures, e.g., by Claisen condensation and its many related methods. Oxidations of β-dicarbonyl compounds **6** to yield this type of alcohols **7** therefore are an extensively investigated field.

This short review summarizes literature known oxidations following Scheme 2, which are classified by the oxidants.

2 Oxidation with Peracids (Rubottom Oxidation)

The reaction of peracids with β-diketones and β-oxo esters, respectively, well-known since the middle of the last century, in general, afforded complex reaction mixtures. In 1958, α-hydroxy-β-diketone **8b** was successfully isolated for the first time in 32% yield from the reaction mixture of 4-methyl-3,5-heptanedione **8a** and monoperphthalic acid.[6] Analogous experiments with other diketones or peracids, however, did not give isolable amounts of the α-hydroxylated products, but led to unspecified decomposition. β-Oxo ester **9a** reacted with peracetic acid to give alcohol **9b** in 10%



Scheme 1. Some examples of the α-hydroxy-β-dicarbonyl moiety in biologically active compounds.

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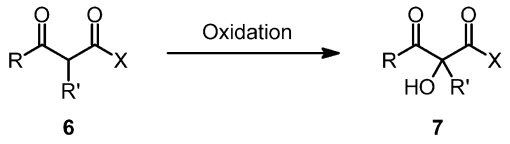
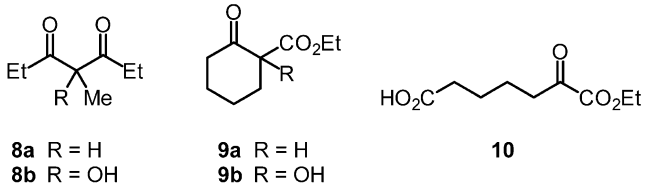
Jens Christoffers (*right*) was born in Germany in 1966. After receiving his Diploma from the Universität Marburg (Germany) in 1992 he moved together with Prof. K. H. Dötz to Bonn (Germany), where he completed his doctorate in 1994 on Fischer carbene complexes and Pauson–Khand reactions. He got in touch with zirconocene catalysis during a postdoctoral stay with Prof. R. G. Bergman in Berkeley (USA). In 1996 he started his independent career at the Technische Universität Berlin (Germany) and finished his Habilitation with Prof. S. Blechert in 2000. He has been an Associate Professor at the Universität Stuttgart (Germany) since 2001. His current research interests are in the fields of asymmetric catalysis, synthesis of heterocyclic compounds and catalytic oxidation reactions utilizing molecular oxygen.

Thomas Werner (*left*) was born and grew up in Berlin (Germany). After having received his Diploma from the Technische Universität Berlin he moved with Prof. Christoffers to the Universität Stuttgart, where he is presently finishing his PhD work on cerium-catalyzed oxidation reactions.

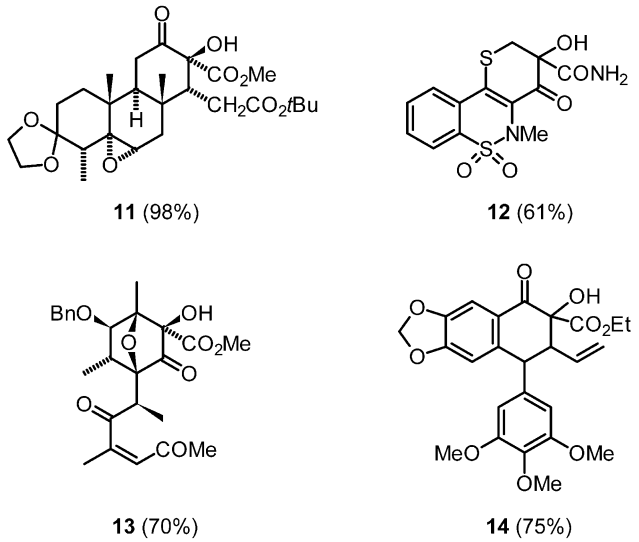
Angelika Baro (*centre*) was born in Stadtoldendorf (Germany). She studied chemistry at the Georg-August-Universität Göttingen (Germany), where she received in 1987 her PhD degree in Clinical Biochemistry under supervision of Prof. H. D. Söling. Since 1991 at the Institut für Organische Chemie, Universität Stuttgart, she is responsible for scientific documentation and publication.



Scheme 2. α-Hydroxylation of β-dicarbonyl compounds.



Scheme 3. Oxidation of β-oxo esters **8a** and **9a** with peracids.



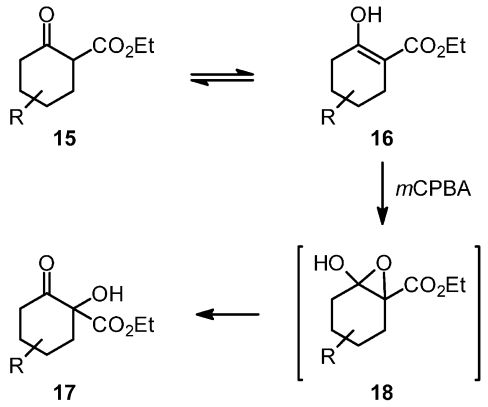
Scheme 4. Direct α-hydroxylation with *m*CPBA according to refs.[8–11]

yield. This conversion always resulted in the open-chain tricarbonyl compound **10** as the major product (Scheme 3).[7]

In a few cases, however, the direct hydroxylation of derivatives of the six-membered ring β-oxo ester with *m*CPBA led to products **11 – 14** in good to high yields (Scheme 4).[8–11]

It is striking that six-membered ring β-oxo esters exist in these four examples, a case in which the enol form **16** dominates the tautomeric equilibrium. An oxidation mechanism *via* hydroxy-epoxide intermediate **18** (Scheme 5) is generally accepted in the literature, however, with one exception discussed later in Section 4, this intermediate could not be characterized so far.

The mechanism shown in Scheme 5 may be regarded as a one-pot variant of a sequence known as Rubottom



Scheme 5. Proposed mechanism of the α-hydroxylation with *m*CPBA.

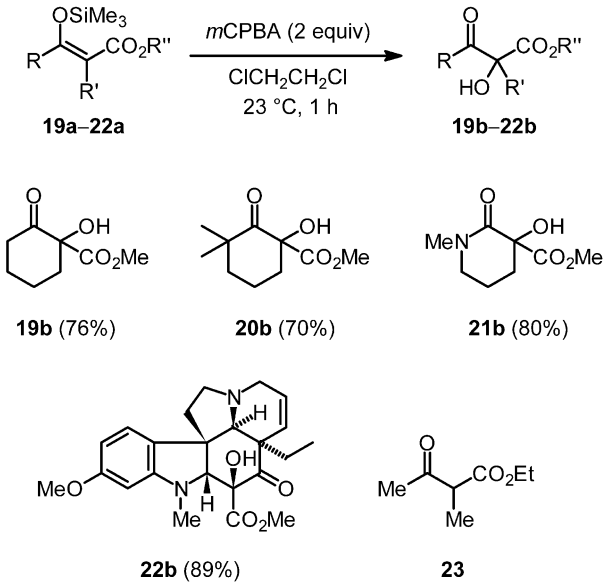
oxidation, in which a silyl enol ether undergoes a hydrolytic rearrangement to the α-hydroxy carbonyl compound after epoxidation.[12] This sequence can be applied without any difficulty to cyclic β-dicarbonyl compounds, as demonstrated for some examples in Scheme 6.[13] In the synthesis of the indole alkaloid vindoline (**5b**), the structure of which is shown in Scheme 1, the Rubottom oxidation was employed to generate the hydroxylated intermediate **22b** in 89% yield.[5,14] In contrast, the acyclic substrate **23** does not give any isolable product.

The Rubottom oxidation is a well established method and reliable on the laboratory scale, but with regard to atom economy, it can hardly be accepted, because stoichiometric amounts of peracid, a base and trialkylsilyl halide are required. Due to the large amounts of waste products, the search for alternative methods, for example, the use of dimethyldioxirane or atmospheric oxygen as oxidants, is still an actual and challenging target.

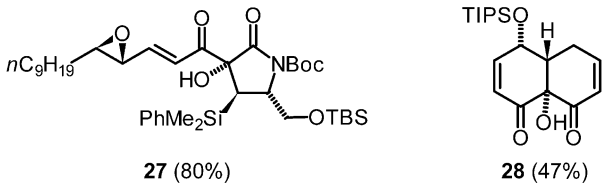
3 Oxidation with Dimethyldioxirane

Dimethyldioxirane (DMD), conveniently prepared from acetone and hydrogen peroxide or persulfates, can be utilized for the epoxidation of various olefins.[15] Some methods are listed in Table 1. If the precursor dicarbonyl compounds are treated with DMD without any additive (method A), several days are required for complete conversion of the starting materials to yield the corresponding alcohols **24 – 26** (Table 1).[16] The reaction is accelerated by addition of one equivalent of fluoride (method B), presumably owing to fluoride ion stabilization of the enol tautomer of the ester/lactone by H bonding. Further improvement was achieved by Adam and coworkers with a substoichiometric amount of $Ni(acac)_2$ (method C).[17]

The combination of the basic acac counterion and the transition metal ion forms *in situ* Ni-diketonate com-



Scheme 6. α-Hydroxylation products **19b – 22b** by Rubottom oxidation of the corresponding silyl enol ethers **19a – 22a**.[13]



Scheme 7. Oxidation with DMD.[18,19]

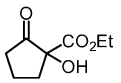
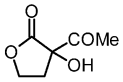
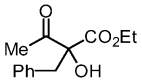
plexes.[17] Barrett and coworkers utilized the $Ni(acac)_2$-catalyzed oxidation with DMD in order to prepare the hydroxy dione **27** (Scheme 7), a precursor in the synthesis of the γ-lactam natural product (−)-pramanicin.[18] By using DMD without any additive Sulikowski et al. obtained the bicyclic α-hydroxy-β-diketone **28** in course of their studies toward the total synthesis of hibarimicinone.[19]

4 Oxidation with Molecular Oxygen

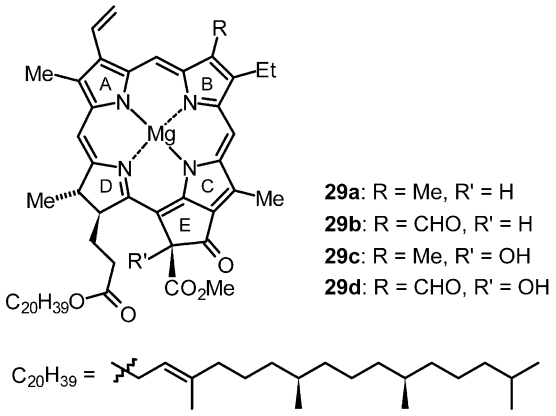
Chlorophyll (Chl) is the green coloring matter in higher plants and plays a central role in the energy uptake from sunlight in the photosynthesis of carbohydrates. It consists of chlorophylls a and b (**29a**, **b**), both having a cyclic β-oxo ester moiety in ring E (Scheme 8).

Chlorophyll is known for a long time to be oxidized spontaneously by atmospheric oxygen in alcoholic solutions. This special kind of oxidation was called "allomerization" by Willstätter,[20] leading commonly to complex mixtures of products known as Chl allomers. Allomerization has been implicated as an early stage reaction in the breakdown of chlorophyll in the natural environment. Considerable effort has been made to

Table 1. α-Hydroxylations using DMD as the oxidant.

Products	Method A		Method B		Method C	
	Time	Yield	Time	Yield	Time	Yield
 **24**	3 d	*ca.* 100%	1 h	85%	3.5 h	> 95%
 **25**	3 d	98%	1 h	85%	1 h	76%
 **26**	3 d	*ca.* 100%	3.5 h	> 95%	4.25 h	78%

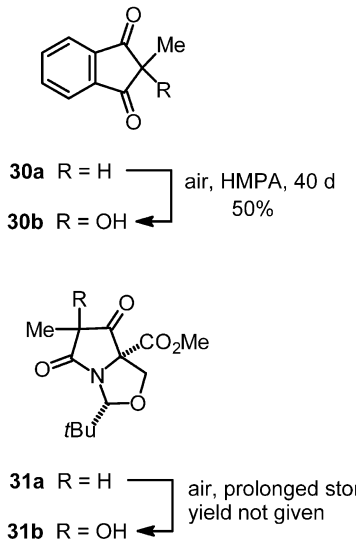
Method A: DMD (3 equivs.) in acetone, 20 °C; Method B: DMD (1 equiv.) in acetone, KF (1 equiv.), 20 °C; Method C: $Ni(acac)_2$ (0.1 equiv.), DMD (*ca.* 1 equiv.), acetone, 20 °C.



Scheme 8. Chlorophylls a and b (**29a**, **b**) and chlorophyll a and b allomers (**29c**, **d**).

elucidate the constitution of Chl allomers[21] and the mechanism for this process.[22] Nowadays, the α-hydroxylated derivatives **29c** and **29d** are established to be one of the two lead products of allomerization.[23] Spontaneous oxidation of β-dicarbonyl compounds by air affording α-hydroxylated products has also been observed in other cases such as **30** and **31**, however, this process usually gave only moderate yields (Scheme 9).[24,25]

The α-hydroxylation of Chl as well as other substrates has been postulated to occur *via* the enol tautomers. The keto-enol equilibrium can be shifted in favor of the enol isomer by H bonding to fluoride ions. This strategy has been utilized for the α-alkylation of β-dicarbonyl compounds.[26] Consequently, the α-hydroxylation with oxygen in the presence of alkali metal fluorides has been developed: First attempts without any photosensitizing reagents gave moderate results for products **32** (57%) and **1** (6%) (Table 2).[27]

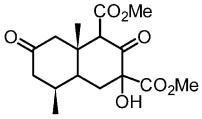
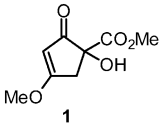
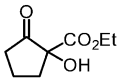
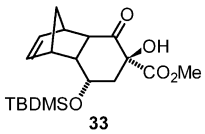
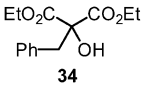
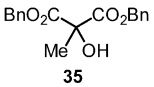
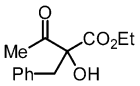


Scheme 9. Examples for spontaneous air oxidation.[24,25]

The procedure was improved by Wasserman et al. by using methylene blue as a photosensitizer to generate $^1O_2$.[28] However, the yield of product **24** is still moderate. Ogasawara applied this protocol successfully to the preparation of precursors like **33** of (−)-shikimic acid and other optically active polyoxygenated cyclohexene derivatives.[29] Watanabe and coworkers were able to prepare α-hydroxymalonates **34** and **35** in high yields with a system of CsF in DMF (Table 2).[30] This protocol, however, is not applicable to obtain α-hydroxy-β-oxo ester **26**. In this case, a substoichiometric amount of Cs_2CO_3 gave optimal results (Table 2).

With regard to economical and ecological considerations the beneficial nature of the oxidant O_2 is spoiled by stoichiometric amounts of a fluoride ion as an additive. Therefore, fluoride-free α-hydroxylations are

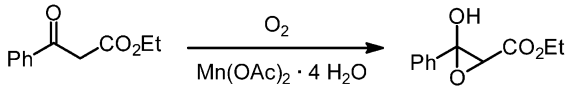
Table 2. α-Hydroxylation of β-oxo esters in the presence of fluoride.

Products	Conditions	Yield	Ref.
 **32**	1 atm O_2, KF (1 equiv.), DMSO, 60 °C, 1 h	57%	[27]
 **1**	1 atm O_2, KF (1 equiv.), DMSO, 60 °C, 1 h, $P(OEt)_3$, reflux, 30 min	6%	[27]
 **24**	1 atm O_2, Bu_4NF (2 equiv.), methylene blue, $CHCl_3$, 5 °C, 2 h	49%	[28]
 **33**	1 atm O_2, KF, $P(OEt)_3$, DMSO, 30 °C	82%	[29]
 **34**	air, CsF (2 equiv.), DMF, 23 °C, 31 h	99%	[30]
 **35**	air, CsF (2 equiv.), DMF, 23 °C, 4 h	92%	[30]
 **26**	air, CsF (2 equiv.), DMF, 23 °C, 4 h air, CsF (0.1 equiv.), DMF, 23 °C, 3 d air, Cs_2CO_3 (0.1 equiv.), DMF, 23 °C, 65 h	30% 50% 75%	[30] [30] [30]

of particular interest. In 1999, an Mn-catalyzed α-hydroxylation with molecular oxygen to yield the cyclic α-hydroxy-β-oxo esters **9b**, **24** and **36** was published.[31] The five- and seven-membered ring products **24** and **36** were isolated in good yield in the presence of 5 mol % $Mn(OAc)_2 \cdot 4\,H_2O$ (Table 3), whereas the six-membered ring alcohol **9b** was obtained in a lower yield due to decomposition under these reaction conditions under formation of the open-chain by-product **10** (see Scheme 3). Unfortunately, the Mn-catalysis failed to convert any acyclic substrate. As an exceptional case, however, the hydroxy-epoxide **40** (Scheme 10) was obtained under the reaction conditions of method A (see Table 3) in low yield from the respective substrate ethyl benzoylacetate **39**. Compound **40** is a stable material under neutral conditions and may be considered as a postulated intermediate in the Rubottom oxidation.

With $CoCl_2$ as the catalyst, also acyclic products such as **37** and **26** are available from the respective β-oxo esters under 1 atm O_2 at 60 °C.[32] In Table 3, both the results of Co- and Mn-catalysis are compared.

From a toxicological point of view, however, the element cobalt can be considered as a little problematic.



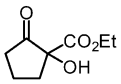
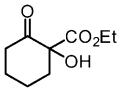
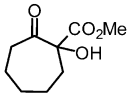
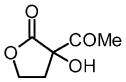
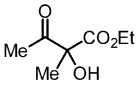
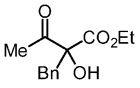
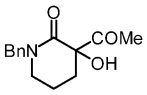
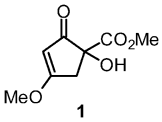
39 **40** (6%)

Scheme 10. Intermediate hydroxy-epoxide **40** in the Mn-catalyzed oxidation.[31]

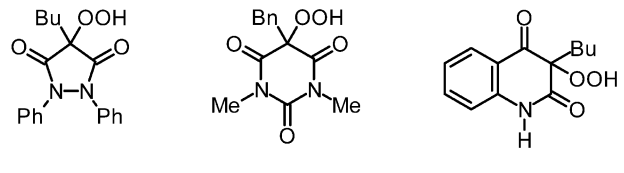
In 2002, the cerium salt ($CeCl_3 \cdot 7\,H_2O$)-catalyzed α-hydroxylation of β-dicarbonyls was reported.[33] In Table 3 some results are compared with the Co- and Mn-catalysis. In summary, the cerium salt can be considered as the optimal catalyst since it is non-toxic and inexpensive. Moreover, conversions proceed at ambient temperature in 2-propanol as the solvent. Generally, good yields are realized at least for cyclic substrates, whereas acyclic products are again accessible in lower quantities.

Very recently, similar aerobic α-hydroperoxidations of heterocyclic 1,3-dicarbonyl compounds are reported to be catalyzed by $Mn(OAc)_3$. Some representative examples are collected in Scheme 11.[34]

Table 3. Metal-catalyzed oxidations to α-hydroxylated products.

Products	Method/Yields		
	A[31]	B[32]	C[33]
 **24**	89%	83% (2 h)	99%
 **9b**	74%	60% (4 h)	59%
 **36**	82%	–	96%
 **25**	–	60% (20 h)	78%
 **37**	–	50% (24 h)	29%
 **26**	–	65% (24 h)	30%
 **38**	–	–	85%
 **1**	–	–	80%[33c]

Method A: 5 mol % $Mn(OAc)_2 \cdot 4\,H_2O$, 1 atm O_2, CH_2Cl_2, 23 °C, 14 h; Method B: 5 mol % $CoCl_2$, 1 atm O_2, MeCN/CH_2Cl_2 (2:1), 60 °C, time given; Method C: 5 mol % $CeCl_3 \cdot 7\,H_2O$, 1 atm O_2, *i*PrOH, 23 °C, 16 h.



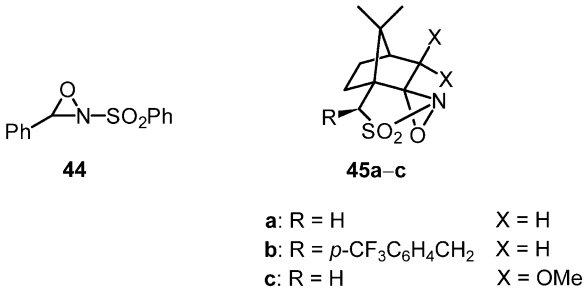
41 (99%) **42** (90%) **43** (57%)

Scheme 11. Oxidation products obtained with 10 mol % $Mn(OAc)_3$, air, AcOH, 23 °C, 2 h.[34]

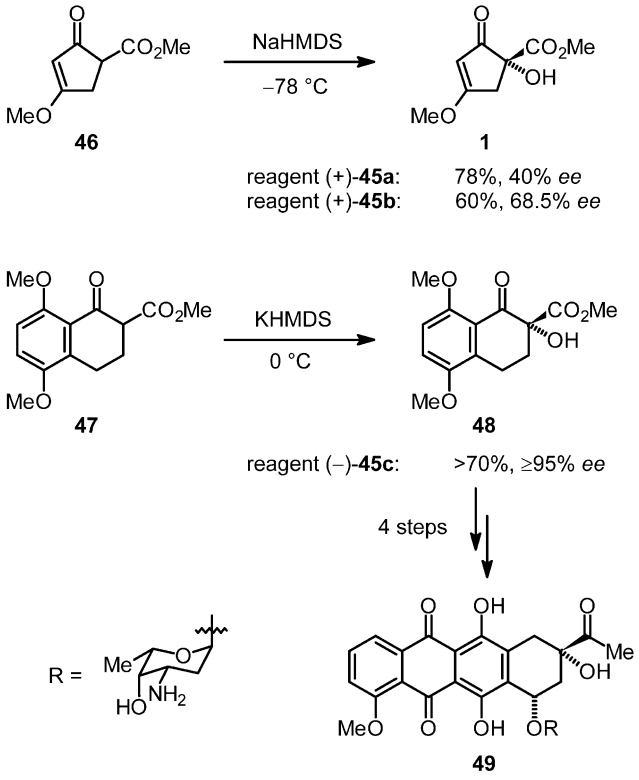
5 Oxidation with Oxaziridines (Davis Reagent)

The Rubottom oxidation is a reliable three-step laboratory methodology for the α-hydroxylation of β-dicarbonyls, however, an enantioselective variant does not exist to date. Also the Mn-, Co-, and Ce-catalyzed processes, utilizing molecular oxygen as the oxidant and therefore being the method of choice with regard to ecological and economical considerations, give only racemic products. When an asymmetric α-hydroxylation is envisioned, the application of an optically active oxaziridine (Davis reagent)[35] is the only available method, though, highly reliable in most cases. Common chiral oxaziridines, which of course can also be applied in their racemic form,[36] are shown in Scheme 12.

Both enantiomeric (camphorylsulfonyl)oxaziridines (+)-**45a** and (−)-**45a** are commercially available reagents, and their application has been reviewed intensively by Davis.[37] Thus, only two examples, the asymmetric hydroxylation of the β-oxo esters **46** and **47**, are given in this article (Scheme 13). The optically active



Scheme 12. Sulfonyloxaziridines for α-hydroxylations.

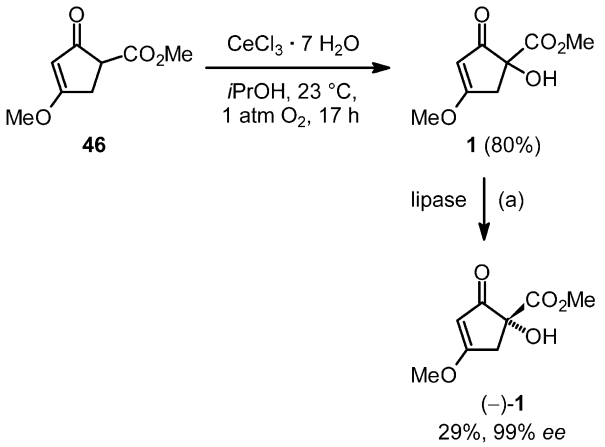


Scheme 13. Asymmetric α-hydroxylations to biologically active compounds **1** and **48**.

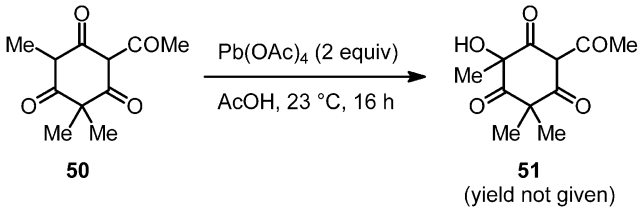
kjellmanianone **1** was obtained with 40% ee by using the oxaziridine (+)-**45a**, while the *p*-trifluoromethylbenzyl-derivatized sulfonyloxaziridine (+)-**45b** gave the natural product **1** with 68.5% ee.[38] Hydroxylation of **47** with reagent (−)-**45c** proceeded with almost quantitative stereoselectivity.[39] Product **48** is the key intermediate in the synthesis of a number of anthracycline antibiotics such as daunomycin **49**, which are common drugs in antitumor combination chemotherapy.

The stereoselective preparation of chlorophyll allomers could be realized with Davis oxaziridines using the concept of double stereodifferentiation.[40]

A novel method involving a cerium salt-catalyzed α-hydroxylation followed by a lipase-mediated saponification/decarboxylation sequence to resolve the racemic



Scheme 14. Alternative route for the preparation of (−)-kjellmanianone **1**. (a) *Candida antarctica* lipase B, toluene/phosphate buffer, 35–40 °C, 48 h.[33c]



Scheme 15. Oxidations using lead(IV).

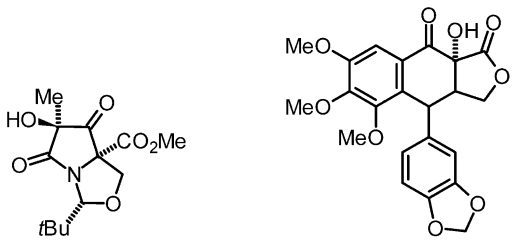
material is a convenient alternative synthetic route to (*R*)-(−)-kjellmanianone **1** (Scheme 14).[33c]

6 Miscellaneous Methods

Lead(IV) acetate reacts with ketones under formation of α-acetoxy derivatives.[41] α,β'-Unsaturated compounds can be obtained from β-oxo esters by *in situ* elimination of acetic acid.[42] In some cases, however, α-hydroxylated products are isolated as shown in Scheme 15.[43]

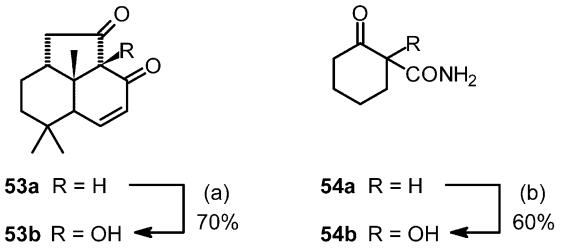
The stable molybdenum peroxide reagent MoO_5 · pyridine · HMPA (MoOPH) was first reported by Mimoun[44] and was later established by Vedejs et al. for the conversion of enolates to α-hydroxy ketones.[45] According to Anderson and coworkers, HMPA can be replaced by DMPU, which of course is a safer alternative.[46] Although MoOPH was reported to fail in the oxidation step in the synthesis of hyperolactone A,[36a] the method was successfully applied for the α-hydroxylation of β-dicarbonyl compounds in at least two cases (Scheme 16).[25,47]

Lactone **53a** has been oxidized selectively with OsO_4, together with NMO as a stoichiometric oxidant, to yield product **53b** (Scheme 17). This α-hydroxylation by Os(VIII) is, however, an exceptional case. The authors



31b (31%) **52** (90%)

Scheme 16. Oxidation with MoOPH as oxidant.



Scheme 17. α-Hydroxylations using (a) OsO_4/*N*-methylmorpholine *N*-oxide; (b) NaOCl (1 equiv.), H_2O, 23 °C.

actually intended to functionalize directly the double bond by dihydroxylation.[48]

Attempts to perform a Hofmann degradation of β-oxo amide **54a** with NaOCl afforded the α-hydroxylated product **54b** in 60% yield (Scheme 17).[49]

The utilization of iodine in combination with sunlight and/or air has been reported twice. However, the oxidations, being postulated to proceed *via* a radical mechanism, gave low yields and were accompanied by by-product formations.[50]

7 Conclusions

With regard to ecological and economical concerns, the direct α-hydroxylation of β-dicarbonyl compounds with molecular oxygen catalyzed by Mn, Co or Ce salts is the procedure of choice. However, these methods are mostly restricted to certain substrates such as carbo- and heterocyclic compounds.

The to date recommended laboratory method is the three-step sequence consisting of deprotonation, silyl enol ether formation, and epoxidation followed by acidic hydrolysis. This so-called Rubottom oxidation is safe and reliable in most cases, though it is time-consuming and requires stoichiometric amounts of several reagents. Therefore, it cannot compete with the direct metal-catalyzed air oxidation with regard to atom economy.

The only available asymmetric method uses optically active sulfonyloxaziridines. These reagents developed by Davis also need stoichiometric deprotonation prior to oxidation, and the stereoselectivity is not sufficient in all cases. A tedious optimization of the chiral reagent is often necessary.

As an outlook, a method for the catalytic, aerobic, asymmetric α-oxidation of β-dicarbonyl compounds still needs to be developed.

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