Efficient and flexible synthesis of chiral γ- and δ-lactones†

Andreas Habel and Wilhelm Boland*

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An efficient and highly flexible synthesis for chiral γ- and δ-lactones with high enantiomeric purity is described (>99% ee and 57–87% overall yield). The protocol involves alkylation of chiral 1,2-oxiranes with terminally unsaturated Grignard reagents. Subsequent oxidative degradation (OsO_4–Oxone) of the terminal double bond from chiral alk-1-en-5-ols and alk-1-en-6-ols affords 4- or 5-hydroxy acids and γ- and δ-lactones after acidic workup. The flexibility and efficiency of the protocol is illustrated by the synthesis of several alkanolides and alkenolides, hydroxy fatty acids and dihydroisocoumarins.

Introduction

γ- and δ-Lactones or natural products with γ- and δ-lactone substructures are widespread and many of them display pronounced biological activities as attractants for pollination[1] and seed germination stimulants.[2] γ- and δ-Lactones also act as pheromones,[3] antiseptics,[4] allergens,[5] or even as cardiotonic compounds.[6] Lactones are important flavor and aroma constituents and are extensively used as food additives and in perfumery. For example, 4-butylbutanolide occurs in the flavour of apricot, raspberry, hazelnut, strawberry, tea, and exhibits a sweet, creamy dairy flavour with fatty and oily coconut nuances that is recognised down to 7 ppb. A similar low threshold displays 4-octylbutanolide, a characteristic flavour component of apricot, beer, peach, pineapple, rum, and strawberry.[7–9] Also microorganisms are an important source for γ- and δ-lactones.[10,11]

In almost all cases, the biological activity of the compounds is intrinsically linked to their configuration, which underlines the necessity for efficient and flexible routes to chiral lactones. Since the lactone moiety represents a bifunctional structural element in which both functions can be selectively elaborated, lactones also represent valuable building blocks for synthesis.

Enantiomerically pure alkanolides are readily available by a multitude of biotransformations using lipases,[12–16] Baeyer–Villiger oxidases,[17,18] amidases,[19] nitrilases[20] or yeasts.[21] Typical asymmetric syntheses[22] utilise the enantioselective hydrogenation[23] or reduction[24] of γ-ketoacids, the ring-opening of chiral terminal epoxides with 1-morpholino-2-trimethylsilyl acetylene,[25] silver(I)triflate catalysed intramolecular additions of hydroxyl or carboxyl groups to double bonds,[26] or asymmetric Bayer–Villiger oxidations using planar-chiral bisflavin catalysts.[27]

Highly functionalized alkanolides can be obtained by a Reformatsky type of reaction of α-hydroxy ketones with indium enolates.[28] For a recent review see ref. 29.

Department of Bioorganic Chemistry, Max Planck Institute for Chemical Ecology, Hans-Knoell-Str.8, 07745-Jena, Germany. E-mail: boland@ice.mpg.de; Fax: +49 3641 571200; Tel: +49 3641 571202

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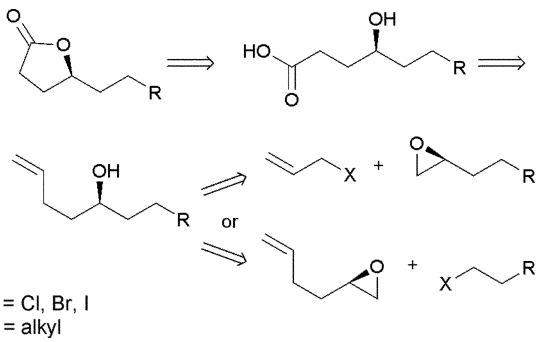
Here we report a fast and flexible strategy for the highly enantioselective synthesis (≥99% ee) of γ- and δ-lactones, that can also provide hydroxy fatty acids and substituted dihydroisocoumarins.

Results and discussion

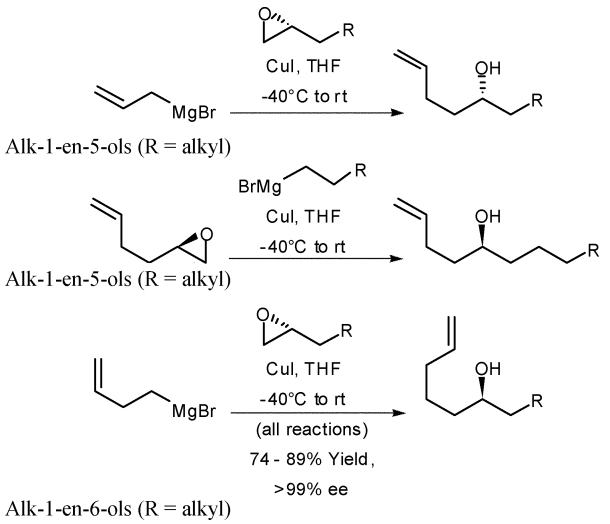
The synthetic approach is illustrated in Scheme 1. Key steps of the protocol are the (i) regioselective alkylation of terminal oxiranes with terminally unsaturated Grignard reagents, and the (ii) chemoselective oxidative cleavage of the resulting terminally unsaturated secondary alcohols to hydroxy acids, which can be cyclized to γ- and δ-lactones by brief treatment with acid during work-up. The chemoselective oxidation of the terminal double bond without simultaneous oxidation of the secondary alcohol[30] is the most important improvement of the sequence and avoids protective group manipulations. Unlike previous protocols using ozonization[31,32] or osmoylation[33] followed by oxidative cleavage of intermediates, the current method proceeds as a single step operation.



Scheme 1 Protocol for the synthesis of chiral alkanolides.

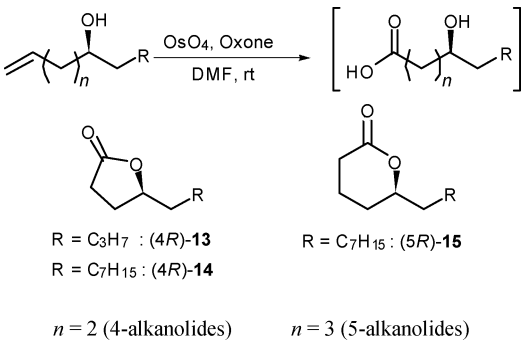
Due to the ease, efficiency and compatibility of the hydrolytic kinetic resolution (HKR) of terminal epoxides with other functional groups following the Jacobson protocol, a broad range of the chiral oxiranes is accessible with high ee (>99%).[34,35] Their subsequent alkylation with terminally unsaturated Grignard reagents in the presence of Cu(I)[36] proceeds exclusively at C(1) and provides the corresponding terminally unsaturated secondary alcohols in high yields and with complete retention of the ee of the starting oxirane (>99%).

To generate the different ring sizes of γ- and δ-lactones, the terminal oxiranes are alkylated with either 1-propenyl- or 1-butenyl Grignard reagents in the presence of (7–10 mol%) cuprous iodide. Alternatively, the alk-1-en-5-ols can be obtained by addition of alkyl-Grignard reagents to 1,2-epoxy-5-hexene **2** (Scheme 2).



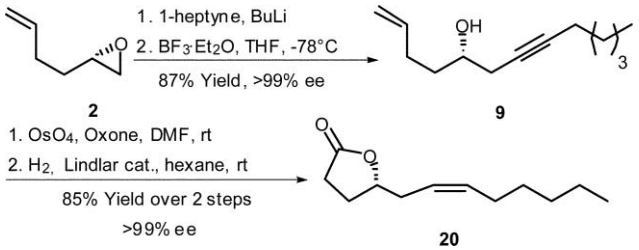
Scheme 2 Alkylation of chiral terminal oxiranes with alkenyl-Grignard reagents.

The recently reported oxidative cleavage of terminal double bonds with catalytic amounts of OsO_4, promoted by Oxone as a co-oxidant, allowed a straightforward and direct conversion of the alk-1-en-4-ols or alk-1-en-5-ols into 3- or 4-hydroxy acids without concomitant oxidation of the secondary hydroxy group.[30] Yields were generally high (81–97%) and the resulting hydroxy acids could be readily cyclized to the corresponding lactones by acidic work-up[37] (Scheme 3).



Scheme 3 Oxidative cleavage of the terminal double bond.

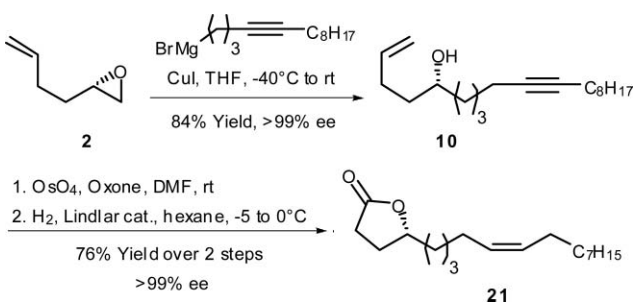
Unlike previous methods for the oxidative cleavage of olefins, the procedure of Travis *et al.* proceeds directly to carboxylic acids, without the intermediacy of 1,2-diols. The whole sequence does not affect the chiral centre of the secondary alcohol, and (*R*)-tridec-1-en-5-ol yielded (*R*)-γ-dodecalactone **14** with complete retention of configuration. Accordingly, the configuration at C(2) of the starting oxirane is preserved in the lactone target as shown by chiral gas chromatography of the intermediates and products. Since the system OsO_4–Oxone tolerates additional functional groups within the molecule such as alcohols, ethers, aromatic rings, esters and, most importantly, alkynes, this opens a direct route to unsaturated lactones and hydroxy acids. For example, (4*S*,6*Z*)-dodecenolide (Scheme 4), previously isolated as major compound from the fungus *Fusarium poae*[38] and the fungus *Sporidiobolus salmonicolor*[39] was obtained in 74% overall yield from (*S*)-1,2-epoxy-5-hexene **2** *via* alkynylation with heptynyl lithium and oxidative cleavage of the terminal double bond followed by hydrogenation.



Scheme 4 Synthesis of (4*S*,6*Z*)-6-dodecen-4-olide.

The alkynylation of the oxirane was achieved according to Yamaguchi and Hirao[40] in the presence of $BF_3 \cdot Et_2O$ at −78 °C and provided the secondary alcohol in 87% isolated yield and >99% ee.

A second example for an olefinic lactone is outlined in Scheme 5 illustrating the synthesis of (4*R*,9*Z*)-octadec-9-en-4-olide **21** (micromolide). Micromolide has been identified as the female sex pheromone of the currant stem girdler *Janus integer*[41] and has been extracted from the stem bark of the Rutaceae *Micromelum hirsutum*.[42] The compound exhibits potent *in vitro* activity against *Mycobacterium tuberculosis* (H37Rv). Alkylation of (*S*)-1,2-epoxy-5-hexene **2** with tridec-4-ynyl magnesium bromide in the presence of Cu(I) afforded the alkynol **10** in 84% yield.

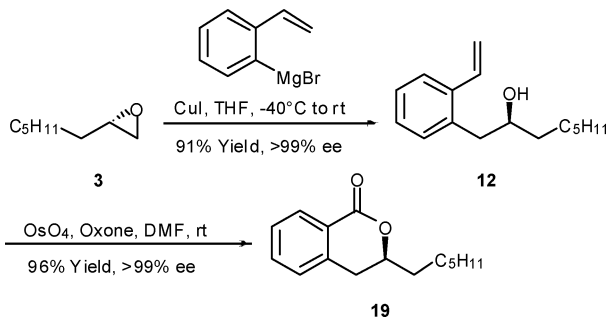


Scheme 5 Synthesis of micromolide.

Subsequent oxidation and hydrogenation afforded micromolide in 64% overall yield in only four steps. A previously reported synthesis required 11 steps and resulted in an overall yield of 14%.[43]

Since the system OsO_4–Oxone also tolerates aromatic systems, the methodology can be also applied to the synthesis of aromatic lactones. Chiral 3,4-dihydroisocoumarins, previously identified as ant trail pheromones,[44] were recently synthesized by lateral lithiation of (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline and alkylation with aromatic or aliphatic aldehydes in two operations and 40–90% overall yield.[45]

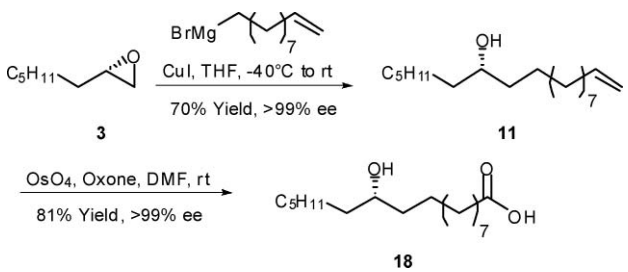
Following our protocol, the (3*S*)-3-hexyl-isochroman-1-one (Scheme 6), can be prepared from commercial starting materials in



Scheme 6 Synthesis of 3,4-dihydroisocoumarins.

two steps and 87% overall yield and 99% ee as shown in Scheme 6 without the need for a kinetically controlled lactonization for enhancement of the ee as described in ref. 45.

By modification of the work-up procedure of the oxidative degradation, chiral hydroxy fatty acids also become available since the ring-closure of lactones ($>C_6$) is no longer spontaneous. For example, (*S*)-12-hydroxyoctadecanoic acid was obtained in only two steps (Scheme 7) from (*S*)-1,2-epoxyoctane and dec-9-enyl magnesium bromide. With acetylenic epoxides or Grignard reagents, the sequence can also be applied to generate unsaturated hydroxy acids.



Scheme 7 Synthesis of chiral hydroxy fatty acids.

The major advantage of the protocol is the easy and efficient access to a wide range of chiral terminal epoxides and Grignard reagents, which allow an efficient and flexible synthesis of the target molecule. In combination with the remarkable tolerance of the OsO_4–Oxone system towards functional groups, in particular secondary alcohols, alkynes and aromatic systems, a direct conversion of the olefinic alcohol into γ- and δ-lactones could be achieved (Table 1). The terminal double bond can be additionally exploited as a valuable masked carboxyl group, allowing further manipulations of the molecule prior to the conversion into the lactone or hydroxy acid.

Table 1 Representative examples

Entry	Compound	ee (%)	Overall yield (%)
1	(4*S*)-Octan-4-olide	>99	70
2	(4*S*)-Dodecan-4-olide	>99	75
3	(5*S*)-Tridecan-5-olide	>99[b]	71
4	(4*S*,6*Z*)-Dodec-6-en-4-olide	>99	74
5	(4*R*,9*Z*)-9-Octadecen-4-olide	>99[b]	64
6	(*S*)-3-Hexyl-isochroman-1-one	>99	87
7	(12*S*)-12-Hydroxy-octadecanoic acid	>99	57

[a] Enantiomeric excess (ee) was determined by chiral gas chromatography (for details see ESI†). [b] ee was determined for alcohol precursors.

Conclusions

In conclusion, we present a general and efficient enantioselective synthesis for alkanolides, alkenolides and hydroxy fatty acids (>99% ee) that utilizes only simple and readily available reagents. The procedure provides the target compounds in only three steps, high overall yields and very high enantiomeric excess (≥99%, depending on the ee of the starting oxirane).

Acknowledgements

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