Synthesis of Functionalized 2,3- and 3,4-Dihydropyrans Starting from α-Hydroxycarboxylic Esters *via* RCM

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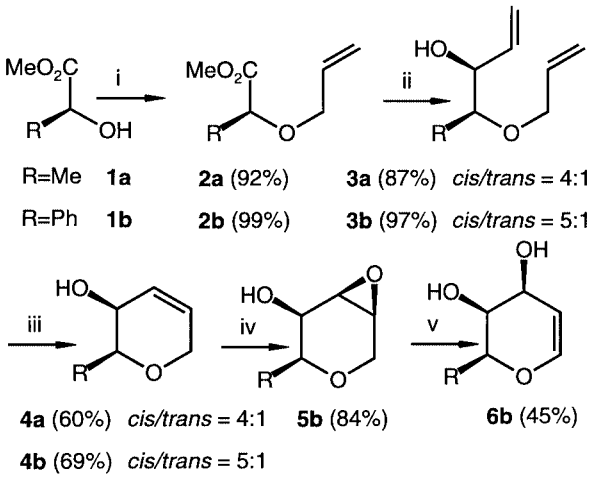
Abstract. α-Hydroxy carboxylic acids and their derivatives are naturally occurring starting materials for the synthesis of functionalized tetrahydropyrans using ring closing metathesis and base induced epoxide rearrangement as key steps. (*S*)-Lactic acid methyl ester has been used as the starting material for the preparation of enantiomerically pure 6-desoxy *C*-glycoside precursors.

Key words: metathesis, pyrans, glycals, epoxidation

Tetrahydropyrans with oxo substituents play an important role in synthetic organic chemistry, as these substructures are found in many natural products with interesting biological properties, such as annonaceous acetogenins,[1] polyether ionophores,[2] and *C*-glycosides.[3-5] The latter class of compounds has found increasing interest over the past years, because many physiologically active natural products with *C*-glycosidic structures have been identified, but there is also a continuous interest in the use of non-natural *C*-glycosides as carbohydrate mimics.[6] Thus, organic chemists have developed a variety of syntheses for these compounds, mostly starting from naturally occurring carbohydrates. Probably the most useful *de novo* synthesis of glycals and carbohydrates is the hetero-Diels-Alder reaction of aldehydes and siloxydienes.[7,8] Metal-catalyzed or -mediated ring closure reactions are less common in this field. Among this group of reactions the ring closing metathesis of dienes[9] turned out to be a very powerful tool over the last few years. Recent examples for the utilization of olefin metathesis for the construction of di- and tetrahydropyran frameworks include the synthesis of spirocyclic dihydropyrans[10] and the utilization of carbohydrates as starting materials for fused or spiroannellated dihydropyrans and -furans.[11]

In this communication we wish to disclose our preliminary results on the utilization of naturally occurring α-hydroxy carboxylic acid[12] derivatives as starting materials for functionalized di- and tetrahydropyrans (Scheme 1).[13]

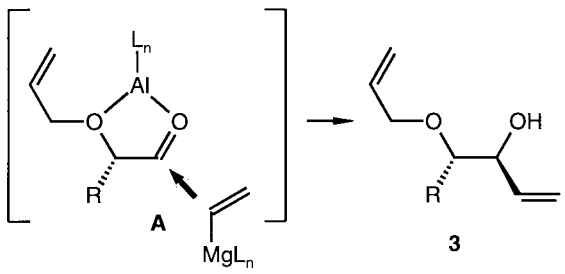
The α-allyloxy ester **2a** was obtained in enantiomerically pure form and very high yield from inexpensive (*S*)-methyl lactate following a literature procedure.[14] Allylation of **1a** with sodium hydride and allyl bromide occurs with complete racemization to give *rac*-**2a** ($[\alpha]^{25}_D = 0°$). Reduction of the ester functionality in **2a** with DIBAL-H and addition of one equivalent of vinylmagnesium chloride in a one-pot procedure yields, with good diastereoselectivity (dr = 4:1), the allylic alcohol **3a**. The relative configuration of **3a** is opposite to the one observed by us for very



i, allylbromide, Ag_2O, Et_2O, r.t.; ii, DIBAL-H, C_2H_3MgCl, Et_2O, -90°C; iii, $Cl_2P(Cy_3)_2Ru{=}CH{-}CH{=}CPh_2$ (3 mol%), DCM, r. t.; iv, Bu-^{t}OOH, $VO(acac)_2$, toluene, 110°C; v, LDA, THF, r.t.

Scheme 1

similar systems, which have been prepared *via* a two-step procedure, i. e. with isolation of the aldehyde.[13] Thus, it is likely that the formation of **3a** *via* the one-pot procedure involves the intermediate formation of a chelate complex **A** of aluminum and the α-allyloxy aldehyde ("Cram's cyclic model") (Scheme 2).[15]



Scheme 2

Ring closing metathesis of **3a** gives dihydropyrans **4a** as an inseparable mixture of diastereomers (*cis*/*trans* = 4:1). The *cis*-configuration of the major diastereoisomer was elucidated by comparison of the coupling constants ^3J(H2-H3), which is 2.3 Hz for the *cis*- and 7.3 Hz for the *trans*-diastereoisomer.

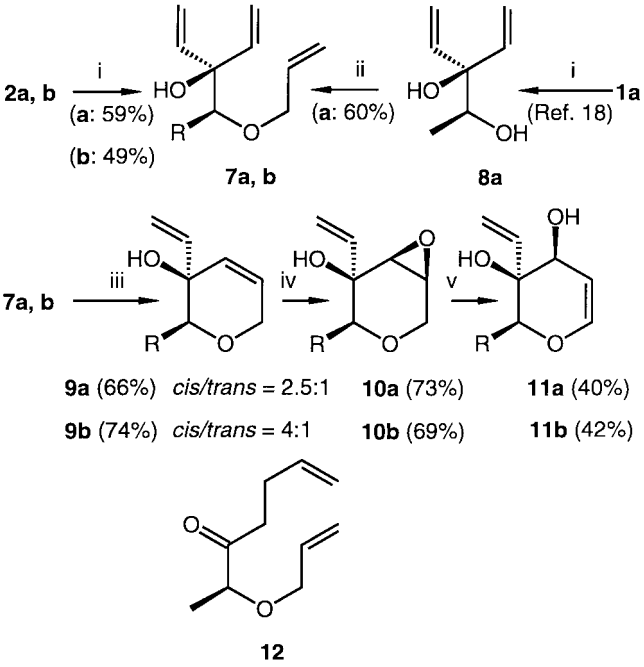
Compound **4a** was used to check whether the reduction-vinylation sequence leading to **3a** occurred without racemization. This was achieved by NMR-shift experiments using $Eu(tfc)_3$ (europium(III)-[3-(trifluoromethyl-hydroxymethylene)camphorate) and $CDCl_3$ as solvent. For reasons of comparison, *rac*-**4a** (obtained from *rac*-**2a** by the sequence described above for the enantiomerically pure material) was also employed in shift experiments. Most conveniently, the doublet for the methyl group is observed: Under conditions where the signals for the enantiomers of *rac*-**4a** are baseline-separated, enantiomerically pure **4a** gives only one doublet, indicating that no racemization occurs during the reaction sequence.

Starting from DL-methyl mandelate, *rac*-**4b** (*cis*/*trans* = 5:1) becomes accessible analogously. In this case it was possible to remove the minor diastereoisomer by careful column chromatography. Dihydropyrans **4** can be readily elaborated into cyclic enol ethers with additional hydroxy functions in the 3- and 4-position. Thus, *cis*-*rac*-**4b** was subjected to a highly diastereoselective substrate directed epoxidation[16] using *t*-BuOOH and $VO(acac)_2$ (dr > 95:5, as only the all-*cis*-diastereoisomer was detected from the H-NMR spectra of the reaction mixture). Base-induced isomerization[17] of *rac*-**5b** in the presence of three equivalents of LDA gives *rac*-**6b** as a single diastereoisomer, indicating that no deprotonation of the benzylic ether occurs.

α-Hydroxy esters **1** may also serve as starting materials for the construction of tetrahydropyrans with a quaternary centre, a structural element which is very common in the polyether ionophores (e. g. salinomycin or lasalocid) (Scheme 3).[2]

Thus, esters **2** were treated with two equivalents of vinyl magnesium chloride leading to the formation of trienes **7**, along with minor amounts of 1,4-addition product **12**, which was only observed for the lactic acid derivative. Formation of the 1,4-adduct **12** can be completely avoided if ester **1a** is first treated with an excess of vinyl magnesium chloride to give the diol **8a**.[18] In the presence of sodium hydride and allyl bromide at 0°C the secondary hydroxyl group is selectively allylated to give triene **7a**. Both routes leading to **7a** occur without racemization, which was proven by NMR shift experiments (using the $Eu(tfc)_3$ reagent and observing the doublets for the methyl group) of the ring closing metathesis products **9a** and *rac*-**9a**. Ring closing metathesis of **7** is a moderately diastereoselective process:[19,20] For both **9a** (dr = 2.5:1) and **9b** (dr = 4:1) the formation of the *cis*-isomer is preferred; elucidation of the relative configuration was achieved by NOESY-experiments.

3,4-Dihydropyrans **9** have been subjected to the vanadium catalyzed epoxidation, which is both regio- (as exclusively the endocyclic double bond is attacked) and stereoselective (only the epoxides with *cis*-configuration relative to the hydroxyl group are formed). Base induced rearrangement of epoxides **10** opens up a path to highly functionalized cyclic enol ethers **11**.[21]



i, C_2H_3MgCl (exc.), Et_2O, -78°C; ii, allylbromide, NaH, THF, 0°C; iii, $Cl_2P(Cy_3)_2Ru{=}CH{-}CH{=}CPh_2$ (3 mol%), DCM, r. t.; iv, Bu^tOOH, $VO(acac)_2$, toluene, 110°C; v, LDA, THF, r. t.

Scheme 3

In conclusion, we have shown that α-hydroxy carboxylic acids are promising naturally occurring starting materials for functionalized di- and tetrahydropyrans using the ring closing metathesis reaction and base induced rearrangements of dihydropyran oxides as key steps. It is noteworthy that the rearrangement of epoxides **5** and **10** can be carried out without protection of the hydroxyl group. Application of the methodology described herein and its extension to other, natural and non-natural α-hydroxy acid derivatives is currently under investigation.

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(21) Representative procedure for the base-induced rearrangement of epoxides **5** and **10**: To a solution of LDA (31 mmol) in THF (40 mL) under an atmosphere of dry argon was added a solution of epoxide **10a** (1.60 g, 10 mmol) in dry THF (15 mL). The mixture was heated to 65°C until the starting material was fully consumed as judged by TLC. Aqueous workup yields 1.58 g (99%) of crude material which consists mainly of **11a**. Purification was only possible with partial decomposition by Kugelrohr distillation (0.60 g, 38%). **11a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.39 (dd, 1, *J* = 6.3, 1.5 Hz), 5.59 (dd, 1, *J* = 17.3, 10.8 Hz), 5.45 (dd, 1, *J* = 17.3, 1.8 Hz), 5.29 (dd, 1, *J* = 10.8, 1.8 Hz), 4.71 (dd, 1, *J* = 6.3, 2.0 Hz), 4.17 (s(br.), 1), 3.86 (q, 1, *J* = 6.5 Hz), 2.10 (s(br.), 1), 1.18 (d, 3, *J* = 6.5 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.6 (1), 137.6 (1), 116.8 (2), 103.3 (1), 75.6 (1), 71.6 (0), 67.6 (1), 14.2 (3). Compound **6b**: **^{1}H NMR** (400 MHz, C_6D_6) δ 7.24 (d, 2, *J* = 7.5 Hz), 7.09 (dd, 2, *J* = 7.5, 7.3 Hz), 7.00 (t, 1, *J* = 7.3 Hz), 6.20 (d, 1, *J* = 6.0 Hz), 4.54 (ddd, 1, *J* = 6.3, 1.8, 1.8 Hz), 4.47 (s, 1), 4.18 (m, 1), 3.62 (d, 1, *J* = 4.0 Hz), 3.30 (s(br), 2). **^{13}C NMR** (100 MHz, C_6D_6) δ 144.8 (1), 138.6 (0), 128,4 (1), 127.9 (1), 127.0 (1), 103.4 (1), 78.7 (1), 68.6 (1), 65.3 (1).

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