Synthesis of Enantiomerically Pure Dihydrofurans and Dihydropyrans from Common Precursors Using RCM and Tandem RCM–Isomerization

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Abstract: Starting from glyceraldehyde, structurally and stereochemically diverse dihydrofurans and dihydropyrans with a 1,2-dihydroxyethylene side chain can be accessed in few steps via allyl metal addition, O-allylation and ring-closing metathesis (RCM) or tandem RCM–isomerization, respectively. The synthesis of dihydrofurans requires a selective double-bond isomerization on the homoallylic alcohol stage, prior to O-allylation and RCM or RCM–isomerization.

Key words: carbohydrates, isomerizations, metathesis, ruthenium, tandem reactions

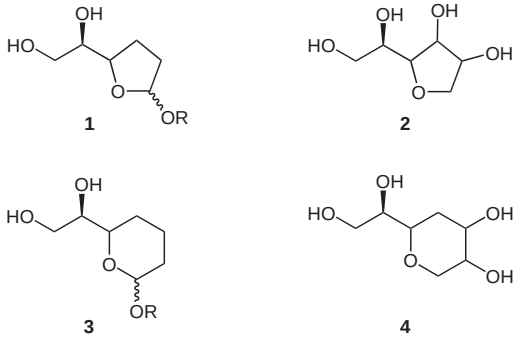

Figure 1 Interesting oxacyclic structures with dihydroxyethylene side-chain

Partially or fully hydroxylated tetrahydrofuran building blocks **1** and **2** with a dihydroxyethylene side chain have attracted considerable interest as constituents in certain disaccharide alditols isolated from seaweed[1] or as intermediates in the total synthesis of complex target molecules such as avermectin,[2] pyragonicin[3] and other annonaceous acetogenins,[4] and certain piperidine alkaloids.[5] HIV-1 protease inhibitors[6] and nucleoside analogues as potential cholesterol lowering agents[7] have also been synthesized using enantiopure building blocks **1** or **2**. Normally, these intermediates are derived from hexitols by cyclization reactions[8–11] or from dianhydrohexitols by ring-opening reactions.[12] The analogous tetrahydropyrans **3** and **4** have also attracted attention from various points of view, e.g. as precursors in the synthesis of the alkaloid conhydrine[13] or as a key structural pattern in various acetogenins.[14] Syntheses based on the use of tartraric acid[13] or hetero Diels–Alder reactions[15] have been published in the literature (Figure 1).

In this contribution we describe a route to the individual diastereomers of regioisomeric dihydrofurans and dihydropyrans which can be elaborated to **1**–**4**, starting from a common precursor, the cyclohexylidene-protected glyceraldehyde[16] **5**. We planned to convert **5** into allylic or homoallylic alcohols by addition of suitable organometallics.[17] Subsequently, the alcohols should be allylated, and the resulting dienes subjected to either RCM[18] or tandem RCM–isomerization sequence.[19,20] This method has been independently developed by us[21–23] and Snapper et al.[24] over the past few years. It relies on the conversion of an olefin-metathesis catalyst into an isomerization catalyst via an organometallic transformation in situ and can thus be considered as an assisted tandem catalysis in the taxonomy recently proposed by Fogg and dos Santos.[25] The required switch from metathesis to isomerization reactivity is achieved by certain additives,[23] which cause a transformation of the Ru-carbene species to the Ru-hydride species. The objective of this contribution is: (i) to demonstrate the usefulness of the tandem RCM–isomerization sequence for the synthesis of enantiopure glycal-type structures[26] and (ii) to illustrate that the combination of metathesis and isomerization reactions in appropriate order allows the selective synthesis of structurally diverse heterocycles starting from a common precursor.

Addition of allyl metal compounds to the isopropylidene analogue of **5** has been investigated some time ago. A significant preference of the *anti*-(*R*,*S*)-isomer was observed if the allylzinc reagent was used in THF.[27,28] In our case both homoallylic alcohols were required and therefore the less selective Grignard reagent was chosen.[16,29,30] The resulting homoallylic alcohols (*R*,*R*)-**6** and (*R*,*S*)-**6** are separable by column chromatography and were separately converted into the known allyl ethers (*R*,*R*)-**7** and (*R*,*S*)-**7**, respectively.[29] Treatment of these dienes with the first-generation Grubbs' catalyst **A**[31] gives the corresponding dihydropyrans (*R*,*R*)-**8** and (*R*,*S*)-**8** in good to excellent yields.[32] Under RCM–isomerization conditions,[23] however, the regioisomeric dihydropyrans (*R*,*R*)-**9** and (*R*,*S*)-**9** were obtained. In both cases, enol ethers **9** were obtained as single regio- and diastereoisomers and the use of 2-propanol and NaOH as additives was found to give the shortest reaction times and highest yields of the desired enol ethers. This indicates that the isomerization step of the tandem sequence is highly regioselective and does not result in any stereochemical scrambling. The α,β-un-

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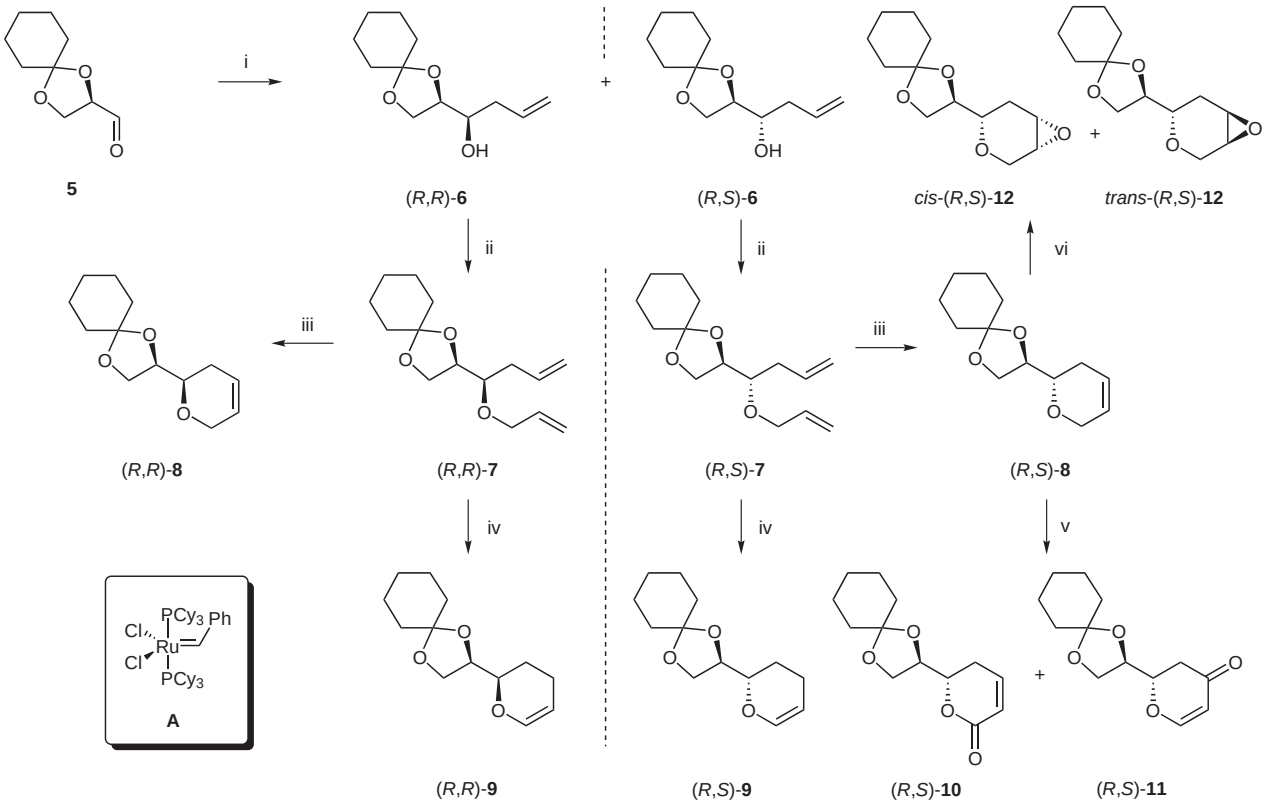


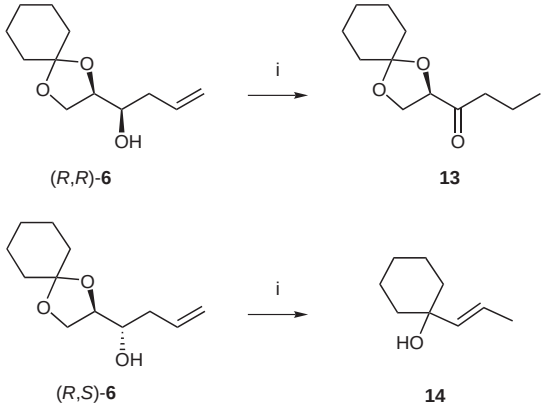
Scheme 1 *Reagents and conditions*: (i) $H_2C{=}CHCH_2MgBr$, Et_2O, –78 °C, H_2O; column chromatography [42% of (*R*,*R*)-**6** and 45% of (*R*,*S*)-**6**]; (ii) $H_2C{=}CHCH_2Br$, THF, 65 °C [81% of (*R*,*R*)-**7** and 99% of (*R*,*S*)-**7**]; (iii) **A** (5 mol%), CH_2Cl_2 [75% of (*R*,*R*)-**8** and 96% of (*R*,*S*)-**8**]; (iv) **A** (5 mol%), toluene, 25 °C, then 2-propanol–KOH, 110 °C [60% of (*R*,*R*)-**9** and 66% of (*R*,*S*)-**9**]; (v) PDC (2.0 equiv), CH_2Cl_2, [**10**/**11** = 10:1, 54% of (*R*,*S*)-**10**]; (vi) MCPBA, CH_2Cl_2, [*cis*-(*R*,*S*)-**12**/*trans*-(*R*,*S*)-**12** = 1:1, 35% of *cis*-(*R*,*S*)-**12** and 35% of *trans*-(*R*,*S*)-**12**].

saturated lactones **10** are also potentially very useful building blocks. The isopropylidene analogues of **10** have previously been obtained as a diastereomeric mixture by ring-closing metathesis of acrylates.[33]

Although significant progress has been made for olefin metathesis reactions involving electron-deficient double bonds, this process is still hampered by the necessity to work at low concentrations. Often Lewis acid additives[34] or the more active second generation catalysts are required to obtain useful rates of conversion,[35] which is a further drawback of the RCM of acrylates. One approach to overcome these difficulties is to convert dihydropyrans **8** into lactones **10** by allylic oxidation, e.g. using Cr(VI) reagents.[36,37] This approach is also in line with the common precursor concept proposed in this contribution and was therefore investigated for dihydropyran (*R*,*S*)-**8**. In the presence of two equivalents of pyridinium dichromate (PDC), (*R*,*S*)-**8** led to the desired lactone (*R*,*S*)-**10** without stereochemical scrambling. However, enone (*R*,*S*)-**11** was formed as an inseparable side product in small amounts. The enone **11** was identified by its characteristic signals in the ^{1}H NMR spectrum (two doublets at δ = 7.29 and δ = 5.38 with a vicinal coupling constant of 6.0 Hz). As RCM and allylic oxidation were conducted in the same solvent, it was an obvious extension to check if both steps could be conducted as a one-pot sequence. Interestingly this approach failed completely and resulted in the quantitative recovery of unchanged dihydropyran **8**. In the case of dihydropyran (*R*,*S*)-**8** the oxidative functionalization of the C=C double bond was demonstrated by dihydropyran oxide formation with MCPBA. The resulting diastereomeric dihydropyran oxides **12** were easily separated by column chromatography and were isolated in good overall yield (Scheme 1).

Next, we planned to synthesize the analogous series of regio- and diastereomeric dihydrofurans. Unfortunately, upon addition of vinyl magnesium chloride to **5**, an inseparable mixture of allylic alcohols was obtained. Various methods of derivatization were then applied to the mixture, but it was not possible to separate the diastereoisomers at this stage. Therefore the possibility was investigated to use the homoallylic alcohols **6** also as starting materials for the dihydrofuran series. To this end, a selective isomerization of the terminal double bond in both isomers of **6** was required. Defined Ru-hydride complexes have been efficiently used to isomerize double bonds in a number of cases.[38,39] However, with respect to 'catalyst economy',[40] we thought that it would be advantageous to use the well-established and commercially available metathesis precatalyst **A** as a precursor for an active isomerization catalyst.[20,41] This approach has been investigated for some examples over the past few years by us[42] and by others.[43] In our experiments we used ethyl vinyl ether as a reagent to convert Ru-benzylidene complex **A**

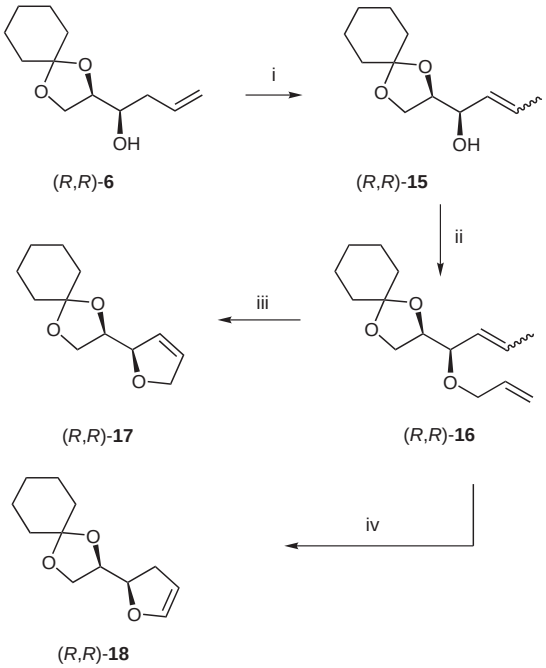
into the hydride complex [RuHCl(CO)(PCy_3)$_2$].[44] The homoallylic alcohols **6** were then treated separately with the in situ generated hydride complex. In a different context we had previously discovered that [RuHCl(CO)(PCy_3)$_2$] is only moderately active in isomerization reactions[23] and therefore we expected a high selectivity for terminal double bonds. However, isomerization of homoallylic alcohols **6** to allylic alcohols was not as straightforward as expected. Not fully unexpected was the formation of ketone **13** from homoallylic alcohol (*R*,*S*)-**6** upon prolonged heating,[45] a process which has often been referred to as redox isomerization.[46] Quite interestingly, the diastereomer (*R*,*R*)-**6** reacted under identical conditions to a fragmentation product **14** (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) **A** (5 mol%), toluene, H_2C=CHOEt, then (*R*,*S*)-**6** or (*R*,*S*)-**6** (42% of **13**, 56% of **14**).

Formation of **14** is a subject of speculation. Obviously, cleavage of the acetal moiety occurs and an oxocarbenium ion is formed, which is subsequently attacked by the vinyl moiety. We assume that a volatile C3-aldehyde is formed as the second cleavage product; however, this could not be detected. Intramolecular transfer of an allyl moiety from homoallylic alcohol (*R*,*S*)-**6** to the oxocarbenium ion, followed by isomerization, appears to be much more likely because such reactions have precedence in the literature.[47] However, such a scenario can be ruled out in this particular case, because monitoring of the progress of the reaction revealed that after one hour (*R*,*S*)-**6** was completely converted into the desired allylic alcohol (*R*,*S*)-**15**, and that **14** resulted from (*R*,*S*)-**15** in a consecutive step. Analogously, isomerization of (*R*,*R*)-**6** under carefully controlled conditions gave the diastereomer (*R*,*R*)-**15**[48] as an *E*/*Z* mixture without formation of ketone **13**. Interestingly, (*R*,*S*)-**15**[48] was formed as a single *E*-isomer. Both diastereomers of **15** were subsequently allylated to the allyl ethers (*R*,*R*)-**16** and (*R*,*S*)-**16**, respectively. Both (*R*,*R*)-**16** and (*R*,*S*)-**16** gave, in the presence of Ru catalyst **A**, the corresponding dihydrofurans (*R*,*R*)-**17** and (*R*,*S*)-**17**, while under tandem RCM–isomerization conditions the enol ethers (*R*,*R*)-**18** and (*R*,*S*)-**18** become selectively available (Scheme 3).[49]

In conclusion, we have shown that oxacyclic products with diverse relative stereochemistries, substitution patterns, and ring sizes can be obtained from just two diastereomeric precursors by using olefin metathesis, isomerization, tandem RCM–isomerization and allylic oxidation as key transformations. Further work to explore the potential of this concept is currently under progress in our laboratory.



Scheme 3 *Reagents and conditions*: (i) **A** (5 mol%), toluene, H_2C=CHOEt, then (*R*,*R*)-**6** or (*R*,*S*)-**6** [74% of (*R*,*R*)-**15**, 58% of (*R*,*S*)-**15**]; (ii) H_2C=$CHCH_2Br$, THF, 65 °C [62% of (*R*,*R*)-**16** and 57% of (*R*,*S*)-**16**]; (iii) **A** (5 mol%), CH_2Cl_2 [70% of (*R*,*R*)-**17** and 56% of (*R*,*S*)-**17**]; (iv) **A** (5 mol%), toluene, 25 °C, then 2-propanol–NaOH, 110 °C [58% of (*R*,*R*)-**18** and 39% of (*R*,*S*)-**18**].

Acknowledgment

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(49) **Synthesis of Cyclic Enol Ethers 9 and 18**: To a solution of the corresponding diene (1.0 mmol) in toluene (10 mL) was added $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (41 mg, 5 mol%). The solution was stirred at 40 °C until the starting material was fully consumed (approximately 30 min, TLC), and 2-propanol (1 mL/mmol) and NaOH (0.25 equiv) were added. The solution was then heated to reflux until the RCM product was completely converted into the enol ether. The reaction mixture was diluted with MTBE and washed with H_2O. The organic layer was separated, dried with $MgSO_4$, filtered, and evaporated. Column chromatography on silica yielded the dihydropyrans or the dihydrofurans. (*R*,*R*)-**9**: $[\alpha]^{23}_D$ –45 (*c* = 0.9, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.41 (d, *J* = 6.0 Hz, 1 H, H6), 4.69 (m, 1 H, H5), 4.18 (ddd, *J* = 6.6, 6.6, 6.6 Hz, 1 H, OH_2CCHO), 4.03 (dd, *J* = 6.6, 8.2 Hz, 1 H, OH_2CCHO), 3.82 (ddd, *J* = 2.7, 6.6, 9.3 Hz, 1 H, H2), 3.75 (dd, *J* = 7.1, 8.2 Hz, 1 H, OH_2CCHO), 1.90–2.17 (2 H, H4), 1.22–1.78 [12 H, H3, $(CH_2)_5$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.6, 110.2, 100.4, 77.0, 75.7, 65.1, 35.9, 34.9, 25.1, 23.9, 23.8, 23.5, 19.4. HRMS: *m*/*z* $[M^+ + Na]$ calcd for $C_{13}H_{20}O_3Na$: 247.1310; found: 247.1308.
(*R*,*R*)-**18**: $[\alpha]^{24}_D$ 51 (*c* = 0.9, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.25 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1 H, H5), 4.89 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1 H, H4), 4.48 (ddd, *J* = 6.8, 6.8, 10.3 Hz, 1 H, H2), 4.03–4.13 (2 H, OH_2CCHO), 3.86 (m, 1 H, OH_2CCHO), 2.72 (dddd, *J* = 2.4, 2.4, 10.3, 15.4 Hz, 1 H, H3), 2.55 (dddd, *J* = 2.4, 2.4, 6.9, 15.4 Hz, 1 H, H3′), 1.40–1.70 [10 H, $(CH_2)_5$]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.9, 109.9, 99.3, 81.2, 76.4, 66.5, 36.4, 34.8, 31.7, 25.2, 24.0, 23.8. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{19}O_3$: 211.1334; found: 211.1331.