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trans-Tetrahydrofurans by OH-Assisted Ru-Catalyzed Isomerization of 2-Butene-1,4-diols

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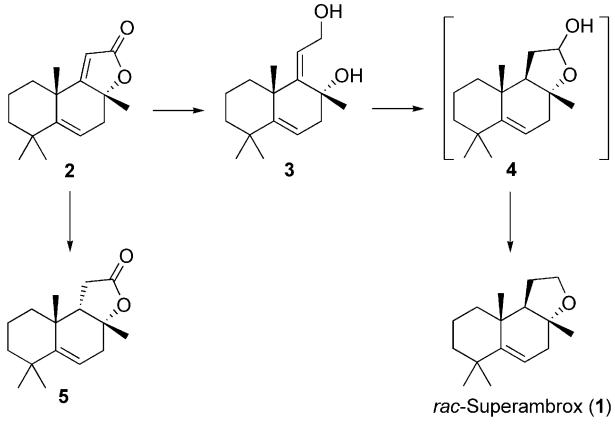
We herein report a general method for the synthesis of 1,2-annulated *trans*-tetrahydrofurans by the OH-assisted Ru-catalyzed isomerization of (*Z*)-2-butene-1,4-diols (using Chaudret's catalyst), followed by reduction of the incipient lactol (using Et_3SiH and Amberlyst 15). Alternatively, the lactol can be oxidized to the corresponding lactone (using Ikariya's catalyst). It was shown by labeling experiments that an addition/elimination pathway is (at least to some extent) operative for the isomerization reaction.

Introduction

Recently, we described a stereoselective synthesis of *rac*-Superambrox (**1**).[1] The *trans* configuration of the tetrahydrofuran ring was obtained by an unprecedented, highly selective OH-assisted Ir- or Ru-catalyzed isomerization of diol **3** and subsequent reduction of lactol **4** by using Et_3SiH[2] (Scheme 1). Conversely, 1,4-reduction of butenolide **2** selectively afforded *cis*-lactone **5**.



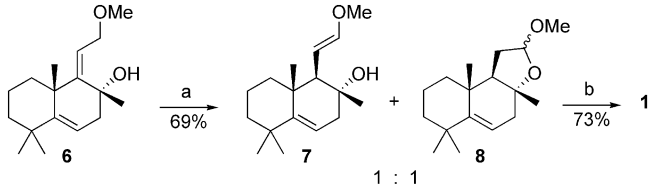
Scheme 1. Synthesis of *rac*-Superambrox by Ir- or Ru-catalyzed OH-directed isomerization of **3**.[1]

The lack of general methods for the synthesis of *trans*-tetrahydrofurans (*trans*-THFs), in particular 1,2-annulated *trans*-THFs that are, in general, more strained than *cis*-THFs,[3] prompted us to study a general approach starting from 2-butene-1,4-diols. Although extensive research activity has been devoted to Ir-,[4] Rh-,[5] and in particular Ru-catalyzed[6–8] isomerizations of allylic alcohols or ethers, an internally assisted stereoselective isomerization by complexation to one or two polar groups has never been reported. Many of the known isomerization catalysts require high reaction temperatures or are only successful with sterically unhindered olefins.

We now report that the OH-assisted Ru-catalyzed isomerization of (*Z*)-2-butene-1,4-diols, using Chaudret's catalyst,[9] is quite general and highly selective for different diol systems and substitution patterns.

Results and Discussion

We found that the OH-assisted Ru-catalyzed isomerization of (*Z*)-2-butene-1,4-diols, using Chaudret's catalyst, also works when the primary OH group is replaced by a OMe group (Scheme 2). Thus, isomerization of **6** afforded stereoselectively (*E*)-enol ether **7** together with acetal **8**. Reduction of **7**/**8** (1:1) by using Et_3SiH and Amberlyst 15[2b] afforded pure **1** in 73% yield.



Scheme 2. The OH-directed isomerization of **6**. Reagents and conditions: (a) $[RuH(\eta^5\text{-}C_8H_{11})_2][BF_4]$ (2.6 mol-%) (Chaudret's catalyst), CH_2Cl_2, room temp., 30 min; (b) Et_3SiH (2.0 equiv.), Amberlyst 15, room temp., 1 h.

Analogously, racemic Ambrox (Cetalox, **11**)[10] and furan **14**,[10b] two constituents of ambergris tincture, could be prepared with excellent stereocontrol from the corresponding lactones **9**[11] and **12**[12] (Scheme 3).

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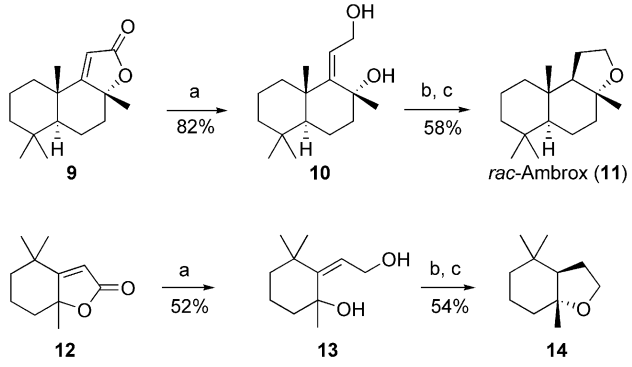
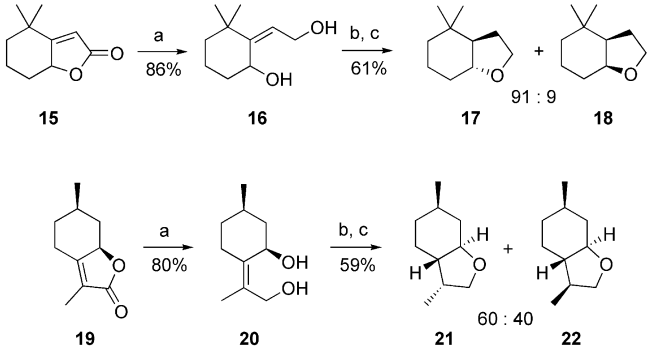


Scheme 3. The OH-directed isomerization of **10** and **13**. Reagents and conditions: (a) $LiAlH_4$ (1.0 equiv.), Et_2O, reflux, 30 min; (b) $[RuH(\eta^5\text{-}C_8H_{11})_2][BF_4]$ (1.0 mol-% for **10**; 0.5 mol-% for **13**) (Chaudret's catalyst), CH_2Cl_2, room temp., 30 min; (c) Et_3SiH (2.0 equiv.), Amberlyst 15, room temp., 1 h.

It should be mentioned that the syntheses of **11** and **14** by acid-catalyzed polyenol cyclizations are less selective, due to concomitant isomerization of the polyenol and the final product.[10]

To investigate whether a diol with a secondary OH group (instead of a tertiary OH group) was still amenable to the same isomerization reaction, alcohol **16**, readily obtained from lactone **15**[13] by reduction, was submitted to the Ru-catalyzed isomerization/reduction sequence (Scheme 4).



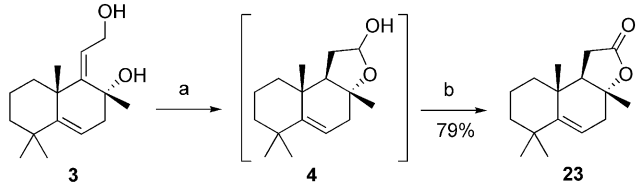
Scheme 4. The OH-directed isomerization of **16** and **20**. Reagents and conditions: (a) $LiAlH_4$ (1.0 equiv.), Et_2O, reflux, 30 min; (b) $[RuH(\eta^5\text{-}C_8H_{11})_2][BF_4]$ (0.5 mol-%) (Chaudret's catalyst), CH_2Cl_2, room temp., 30 min; (c) Et_3SiH (2.0 equiv.), Amberlyst 15, room temp., 1 h.

The overwhelming part of tetrahydrofuran formed was *trans*-THF **17**, accompanied by some *cis*-THF **18**, which may arise from C=C bond isomerization of **16** towards the secondary alcohol function. The same reaction sequence starting from menthalactone **19**,[14] possessing a tetrasubstituted C=C bond is an especially sterically hindered case.

To our delight, the isomerization was complete after 15 min at room temperature, and *trans*-THFs **21** and **22**[15] were formed as the only products, demonstrating that the C=C bond stereoselectively migrates towards the primary alcohol function.

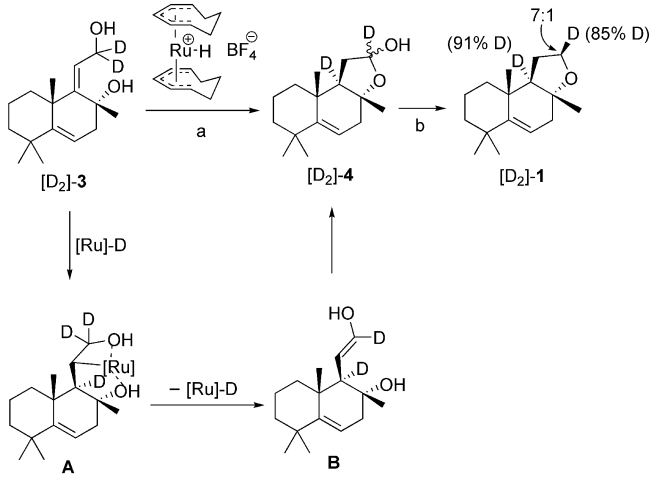
Finally, as [Cp*Ru(PN)] catalysts are known to isomerize allylic alcohols to ketones under mild conditions,[7b] we tested the ability of a [Cp*Ru(PN)] catalyst {PN = $Ph_2P(CH_2)_2NH_2$}[16] to isomerize diol **3** as an access route to **1**. However, smooth dehydrogenation led to lactone **2** (Scheme 1) in 90% yield.[17,18] Indeed, [Cp*Ru{$Ph_2P(CH_2)_2$-NH_2}]Cl under basic conditions (KO*t*Bu) is known to oxidize 1,4-diols to γ-butyrolactones in the presence of acetone.[19] Surprisingly, diol **3** was oxidized even in the absence of a hydride acceptor (acetone), as the reaction was performed in toluene!

This led us to devise a new protocol for the transformation of 2-butene-1,4-diols into *trans*-γ-butyrolactones by a sequential isomerization–dehydrogenation process. Thus, isomerization of diol **3** by using Chaudret's catalyst, followed by dehydrogenation catalyzed by Ikariya's catalyst, led to elusive *trans*-lactone **23** in 79% yield (Scheme 5). In addition, the formation of a trace amount (2%) of doubly unsaturated lactone **2** (Scheme 1) is interesting from a mechanistic point of view (see below).



Scheme 5. *trans*-γ-Butyrolactone **23** by OH-directed isomerization–dehydrogenation of **3**. Reagents and conditions: (a) $[RuH(\eta^5\text{-}C_8H_{11})_2][BF_4]$ (0.5 mol-%), CH_2Cl_2, room temp., 20 min; (b) $[Cp^*Ru(OMe)]_2$ (1 mol-%), $Ph_3P(CH_2)_2NH_2$ (2.1 mol-%), KO*t*Bu (2.0 mol-%), acetone, room temp., 45 min.

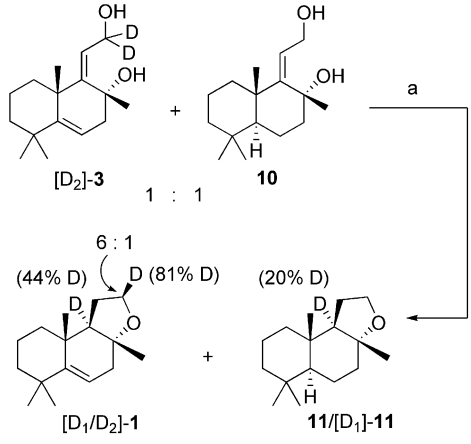
In order to gain further insight into the reaction course, $[D_2]$-**3** (prepared by $LiAlD_4$ reduction of **2**) was submitted to the Ru-catalyzed isomerization reaction. The isomerization occurred with clean 1,3-D shift to afford after silane reduction $[D_2]$-**1** (CHDO center 7:1)[20] (Scheme 6).



Scheme 6. Putative mechanism of the isomerization of 2-butene-1,4-diols. Reagents and conditions: (a) $[RuH(\eta^5\text{-}C_8H_{11})_2][BF_4]$ (0.5 mol-%) (Chaudret's catalyst), CH_2Cl_2, room temp., 30 min; (b) Et_3SiH (2.0 equiv.), Amberlyst 15, room temp., 1 h (66% from $[D_2]$-**3**).

There are three plausible pathways for this OH-directed transition-metal-catalyzed isomerization:[6] an oxidation/reduction by a Ru-complexed α,β-unsaturated aldehyde followed by 1,4-reduction,[7] an oxidative addition that generates a π–allyl ruthenium complex, followed by reductive elimination,[6] or a stereoselective addition of [Ru]-H (or [Ru]-D) leading to **A**, followed by elimination to **B** (Scheme 6). Whereas the two first processes occur with an intramolecular 1,3-H (or D) shift, the addition/elimination process consists of an intermolecular H (or D) transfer.[8]

Because the Ru-catalyzed isomerization works with either ether **6** or diol **3** as substrate, the intermediacy of an enal is not required for effective isomerization (Scheme 2) and the oxidation/reduction pathway is improbable. To distinguish between the other two pathways, a crossover experiment was performed by submitting a 1:1 mixture of the structurally very similar [D_2]-**3** and non-deuterated diol **10** to the Ru-catalyzed isomerization reaction. This resulted in a significant amount of H/D-scrambling (Scheme 7). It can therefore be assumed that the addition/elimination pathway (via **A** and **B**; Scheme 6) is – at least to some extent – operative. Probably the catalyst first coordinates with the two OH groups and with the C=C bond under concomitant reductive displacement of one cyclooctadiene ligand. The required Ru-H(D) species necessary for entering the catalytic cycle is then generated by the dehydrogenation reaction, previously observed as a very minor pathway (see above, formation of trace amounts of lactone **2**).[21,22]



Scheme 7. Crossover experiment with [D_2]-**3** and **10**. Reagents and conditions: (a) [RuH(η^5-C_8H_{11})$_2$][BF_4] (1.0 mol-%), CH_2Cl_2, room temp., 30 min; then Et_3SiH (2.0 equiv.), Amberlyst 15, room temp., 1 h.

We are confident that this reaction will find broad application and initiate new stereoselective Ru-catalyzed isomerization reactions based on polar group assistance.

Conclusion

In conclusion, we have developed a general access route to *trans*-THFs (and *trans*-γ-butyrolactones), which are less accessible than the corresponding *cis*-fused heterocycles.

Experimental Section

21/22: In a first flask, a solution of **20** (1.00 g; 5.88 mmol) in dry CH_2Cl_2 (15 mL; dried with 4 Å MS) was degassed (freezing in liquid N_2, then vacuum, then purging with N_2. The process was repeated twice). A Schlenk tube was charged (in the glove box) with Chaudret's Ru catalyst (12.0 mg, 0.0294 mmol, 0.5 mol-%). The contents of the first flask were added to the catalyst under N_2. The reaction mixture was stirred at room temperature. After 15 min, all starting material **20** was consumed. The formed lactol was treated with Et_3SiH (1.36 g, 1.86 mL, 11.7 mmol) and Amberlyst 15 (2.00 g). The mixture was stirred open to air[2b] for 45 min at room temperature, filtered, concentrated and bulb-to-bulb distilled (oven temp. 100–125 °C, 0.6 mbar) to afford 985 mg of **21** (GC: 30%), **22** (GC: 25%), and $(Et_3Si)_2O$ (GC: 40%). Yield of **21/22**: 59%. Flash chromatography on SiO_2 (50 g; cyclohexane/AcOEt, 95:5) afforded 445 mg of **21/22** (100% pure; 49%).[15]

[D_2]-**1** was prepared in the same manner as **1**.[1] Yield from [D_2]-**3**: 66%. Characteristic signals for [D_2]-**1**: ^{1}H NMR ($CDCl_3$): δ = 3.83 (dd, J = 8, 8 Hz, 1 H; major isomer), 3.95 (m, 1 H, minor isomer) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.7 (t, J = 19.1 Hz, CD), 65.1 (d, CH, t, J = 22.3 Hz, CD] ppm.

Characteristic signal for [D_1]-**11**: ^{13}C NMR ($CDCl_3$): δ = 59.6 (t, J = 19.0 Hz, CD).

Supporting Information (see footnote on the first page of this article): Spectral data for all new compounds.

Acknowledgments

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[11] Prepared in the same way as lactone **2**. For another synthesis of the individual enantiomers, see: R. C. Cambie, B. D. Palmer, *Aust. J. Chem.* **1981**, *34*, 1265.
[12] Racemic dihydroactinidiolide (or tea lactone) **12** is used at Firmenich as a flavor compound. Syntheses: G. M. Rubottom, H. D. Juve Jr., *J. Org. Chem.* **1983**, *48*, 422; K. F. Eidman, B. S. MacDougall, *J. Org. Chem.* **2006**, *71*, 9513 and references cited therein.
[13] Prepared from ethyl(6,6-dimethyl-1-cyclohexen-1-yl)acetate (C. Fehr, B. Winter, I. Magpantay, *Chem. Eur. J.* **2009**, *15*, 9773): (1) *m*-CPBA (1.4 equiv.), CH_2Cl_2, 0 °C to room temp., 1 h (96%); (2) addition of a cooled (–30 °C) solution of formed epoxide in THF to cooled (–30 °C) LDA (1.0 equiv.), THF, 45 min (35%).
[14] (–)-Menthalactone (or Mintlactone) **19** is used at Firmenich as a flavor compound. Review: H. M. C. Ferraz, L. S. Longo Jr., M. V. A. Grazini, *Synthesis* **2002**, 2155.
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[16] For convenience, the catalyst was prepared in situ from $[Cp^*Ru(OMe)]_2$ and $Ph_2P(CH_2)_2NH_2$.
[17] A solution of **3**, $[Cp^*Ru(OMe)]_2$ (1 mol-%), and $Ph_2P(CH_2)_2$-NH_2 (2.1 mol-%) in toluene was stirred at room temp. for 3 h.
[18] Use of Mazet's Ir catalyst (BAr_F-modified Crabtree catalyst)[4b] in THF or Chaudret's Ru catalyst in THF was less efficient in terms of rate and yield.
[19] M. Ito, A. Osaku, A. Shiibashi, T. Ikariya, *Org. Lett.* **2007**, *9*, 1821.
[20] The same result was observed with Crabtree's catalyst.
[21] An analogous dehydrogenation of **6** would lead via an oxenium species to "dehydro-**8**".
[22] The facial selectivity of the Ru species is possibly also governed by steric factors.

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