Enantioselective synthesis of substituted furans by subsequent Cu-catalyzed allylic alkylation/cross-metathesis/intramolecular allylic etherification reactions

Bachelor Research Project

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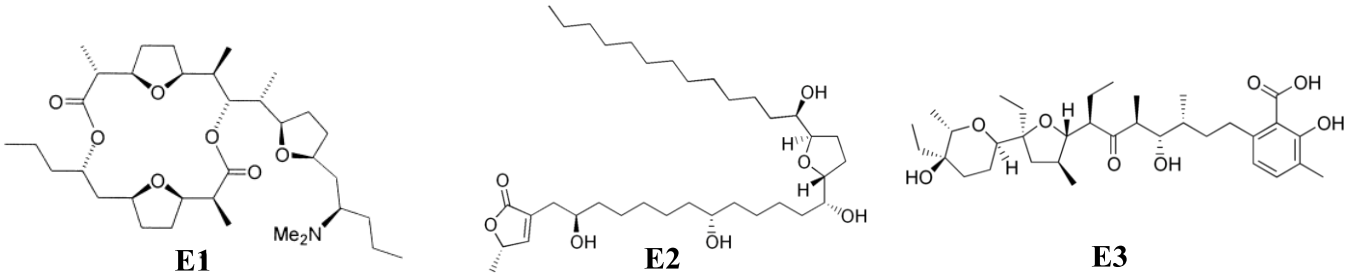
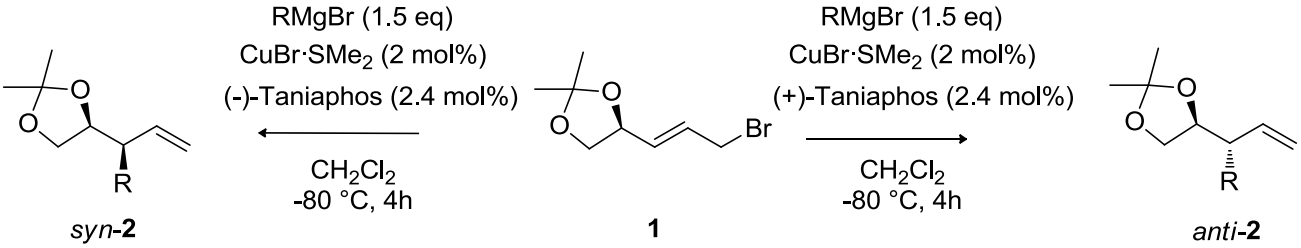
Substituted tetrahydrofurans are frequently found substructures in natural products. (Scheme 1) Examples include molecules from the annonaceous acetogenins family, polyether ionophores, lignans and macrodiolides. These substances exhibit a wide range of biological activities such as antitumor, antihelmic, antimalarial, antimicrobial and antiprotozoal. The importance of these molecules has led to considerable effort in the development of methods for the stereoselective synthesis of substituted tetrahydrofurans.[1]

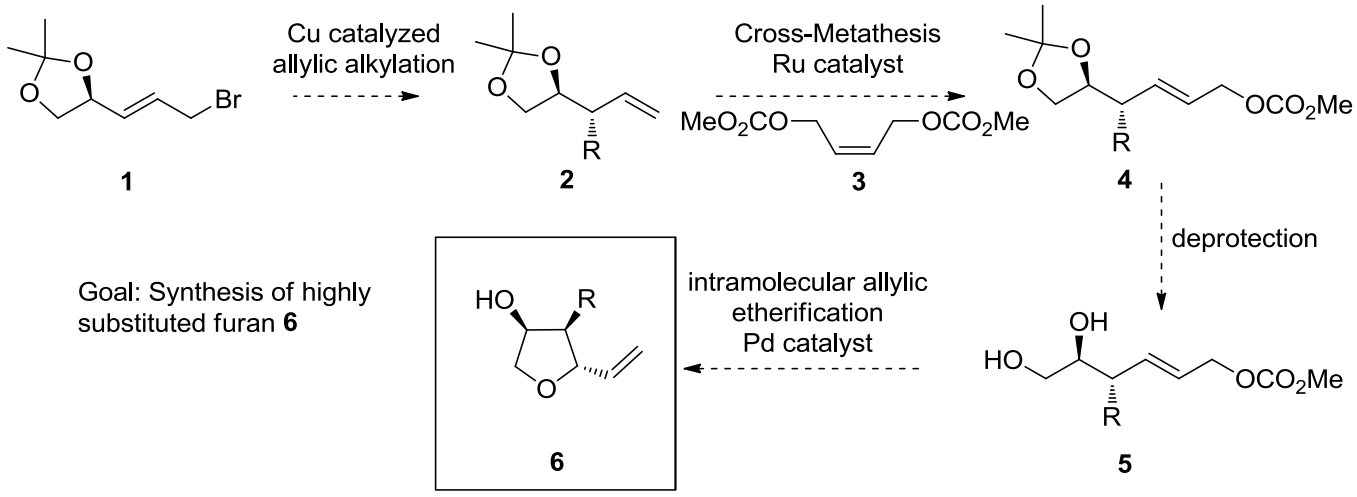


Scheme 1: Examples of natural and pharmaceutical products bearing a furan moiety. **E1**: Paramycin-607 (Antibiotic), **E2:** Annonacin (Blocks mitochondrial complex I), **E3**: Lasalocid A (Antibacterial agent).



Scheme 2: Copper catalyzed allylic alkylation reported by Feringa *et al*.

Feringa *et al*. recently reported an enantioselective copper catalyzed allylic alkylation with Grignard reagents leading to 1,2-hydroxyalkyl moieties **2** (Scheme 2).[2] The Cu-catalysis, using TaniaPhos as chiral ligand, shows high diastereoselecitivy and total regioselectivities starting from allylic bromide **1**. The reaction is catalyst control, and both diastereomers can be obtained selectively by using the corresponding enantiomer of the ligand. In this project **2** is used as starting material for the synthesis of chiral furans as depicted in Scheme 2.

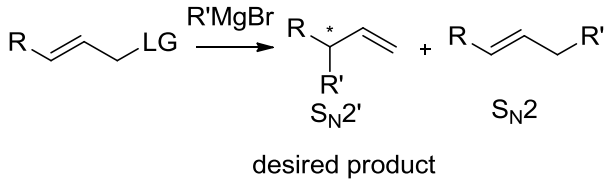


Scheme 3: Project goal and envisioned route for the synthesis of furan **6**.

To obtain furan **6** the following synthetic route was envisioned. The Ruthenium catalyzed cross metathesis of product **2** with dicarbonate **3** would give rise to compound **4**, a suitable material for the intramolecular etherification. For this intramolecular etherification, compound **4** should first be deprotected to diol **5**, after which the intramolecular allylic etherification with a palladium catalyst should be performed. In this final step, the third stereocenter will be installed, giving rise to the highly functionalized furan **6**, bearing a hydroxyl moiety and double bond which can be further functionalized.

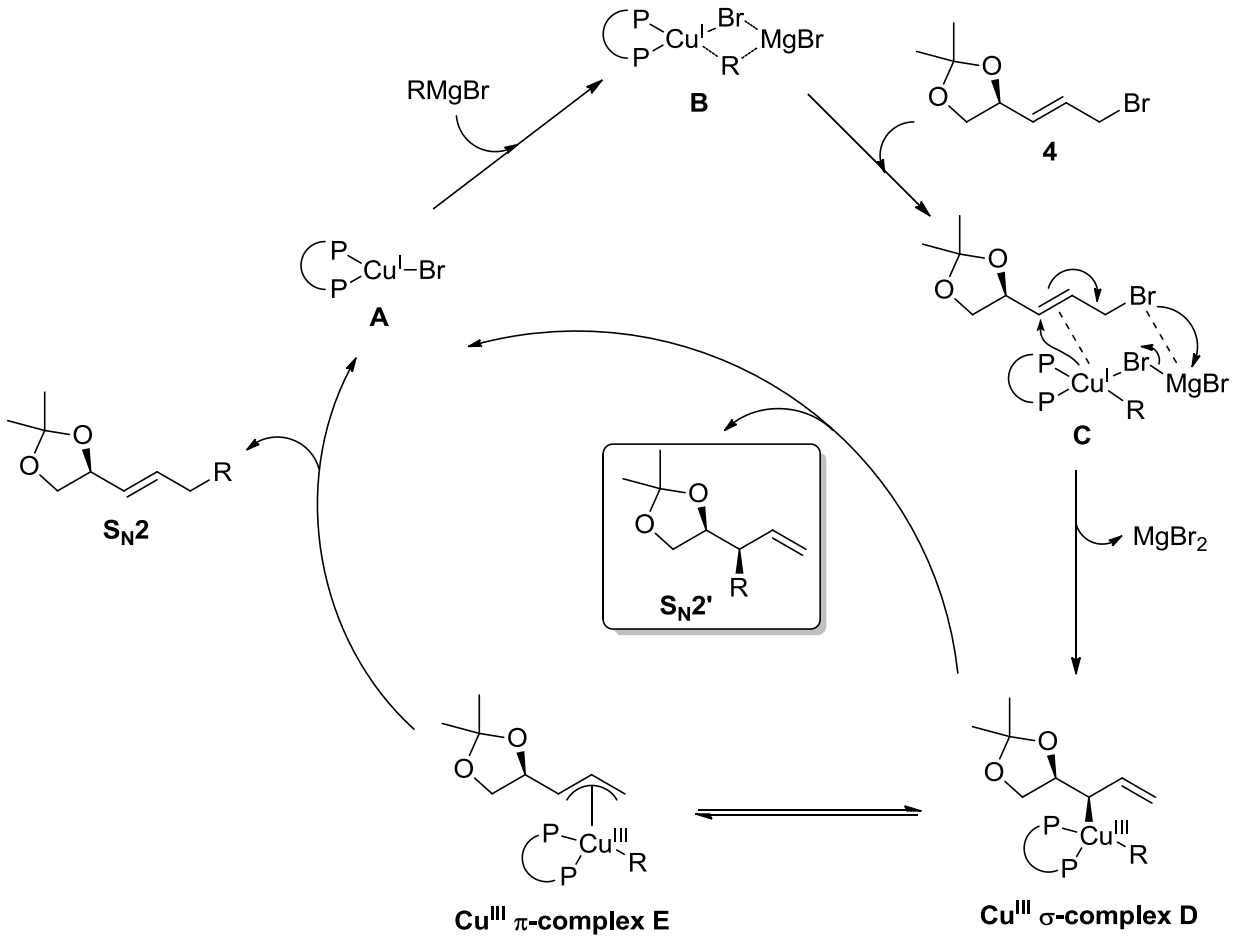
Copper catalyzed allylic alkylation

Copper catalyzed asymmetric allylic alkylation is a powerful tool for the enantioselective formation of C-C bonds. In this reaction, an organometallic reagent attacks on a sp^2 carbon, expelling a leaving group and creating an asymmetrical sp^3 carbon. Chiral ligands for copper are used to control regio- and stereoselectivity. Achieving this control has proven to be challenging. A competing mechanism for the desired S_N2' is the S_N2 mechanism, yielding the linear product (Scheme 4).[3]



Scheme 4: Competing reactions for the asymmetric allylic alkylation.

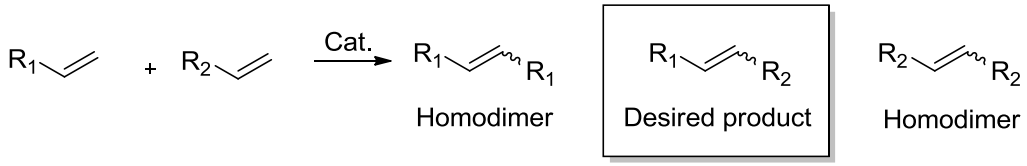
The mechanism for the copper catalyzed allylic alkylation of allyl bromide **1** can be proposed as shown below in the catalytic cycle. (Scheme 5) The first step is the activation of the copper complex with a Grignard reagent to form the active catalyst **B**. The catalyst interacts with the substrate, forming complex **C**. This is followed by oxidative addition and allylic rearrangement to form complex **D**. This can either give rise to the desired product via a formal S_N2' mechanism or the linear product via S_N2 mechanism.[2]



Scheme 5: Catalytic cycle for copper in the allylic alkylation reaction.

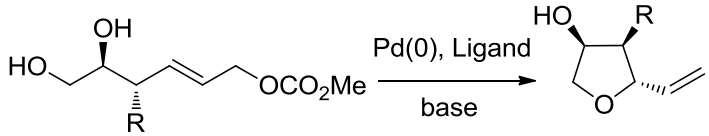
Cross-Metathesis

Cross-metathesis is a convenient method to couple two olefins. Two olefins are coupled using a catalyst which is often ruthenium based. This method however does encounter problems such as low catalyst activity and low selectivity. Selectivity problems includes homodimerization of the starting materials.[4]



Scheme 6: Cross metathesis reaction. Next to the desired coupled product, the homodimers can also be formed.

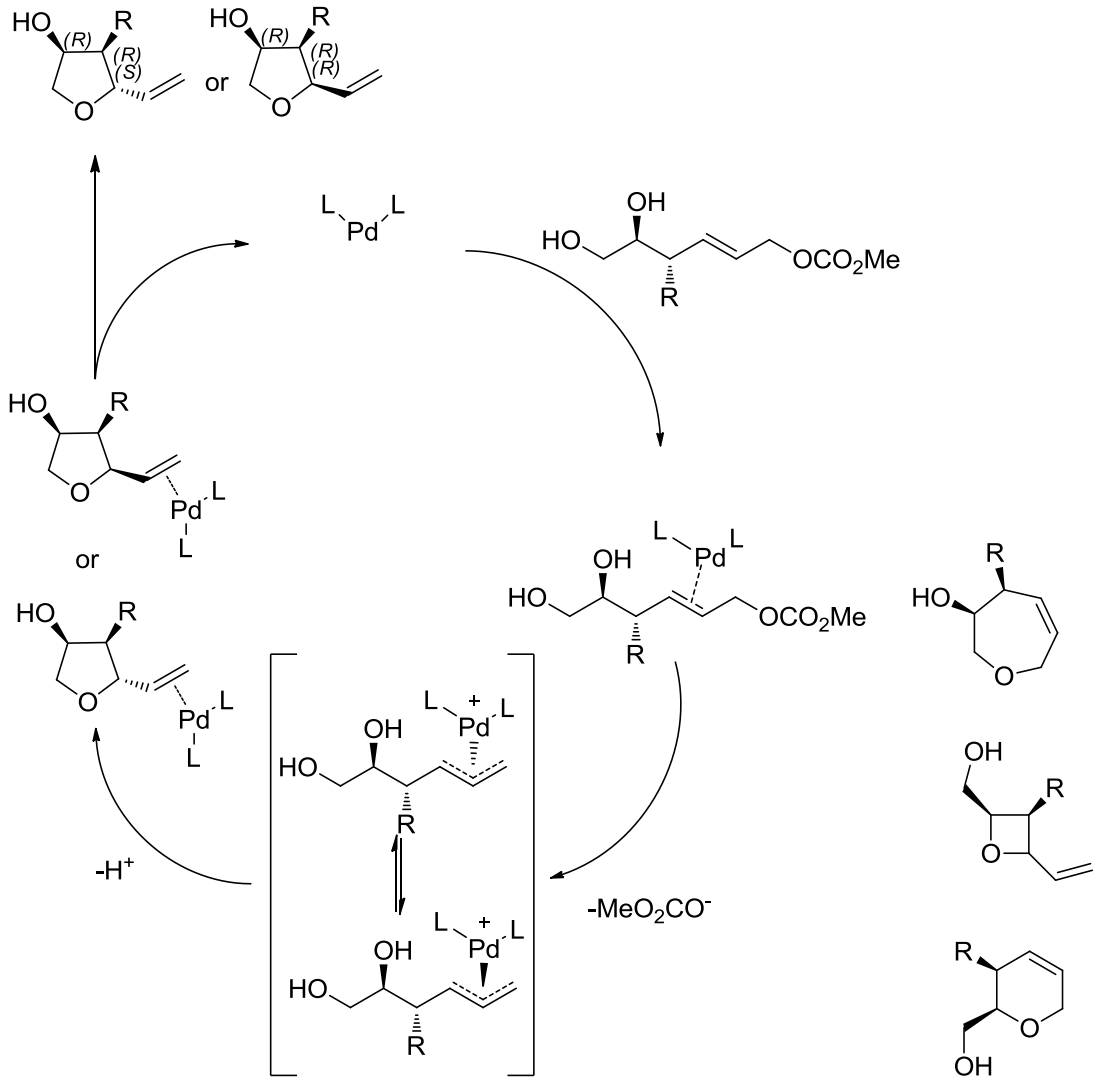
Allylic etherification



Scheme 7: Envisioned product of the palladium catalyzed allylic etherification.

Besides copper catalyzed allylic alkylation, palladium catalyzed allylic alkylation also represents a very useful asymmetric C-C bond forming reaction. In sharp contrast, soft nucleophiles are used when

palladium is used as catalyst, therefore it is also possible to create chiral C-O or C-N bonds. (scheme 7) Again, chiral ligands are used to obtain regio- and stereocontrol. The proposed catalytic cycle for palladium is shown below (scheme 8). The first step is complexation of the catalyst with the substrate. The formed complex is then ionized by elimination of the leaving group to form a π-complex. The π-complex then undergoes a nucleophilic addition which is finally followed by decomplexation to form the product and retrieve the catalyst. In catalytic cycle of paladium, there is an opportunitiy to differentate between diastereomers in each step. During this reaction, it is expected that chirality is set during the complexation step. Most likely the R group will direct the palladium complex in a way that it is *anti,* relative to the R group. This will lead to the (*R,R,S*)-furan.[5]



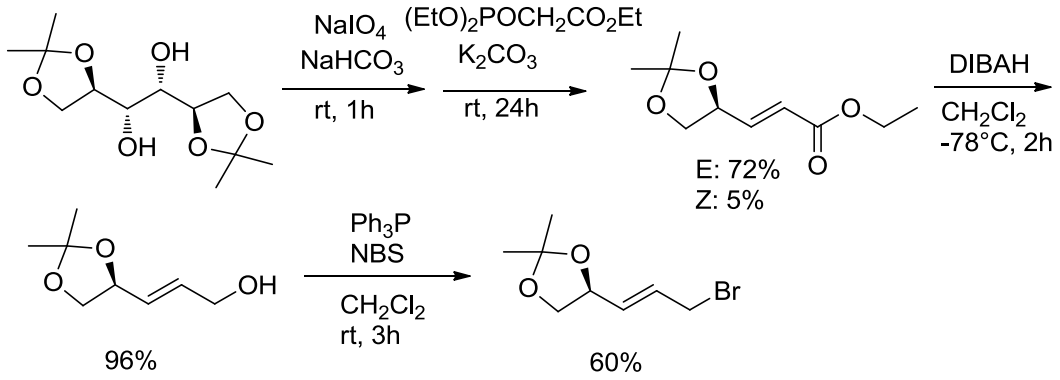
Scheme 8: Catalytic cycle of palladium in the allylic etherification, with possible side products (right).

Next to both stereoselectivity, regioselectivity has to be taken in account, as there are other possible side-reactions that might occur. There are two nucleophiles present: The primary oxygen, which can either give a five membered ring or a seven membered ring, and the secondary oxygen, which can either give a four membered ring or a six membered ring. If the primary oxygen attacks, the five membered ring is thermodynamically favored relative to the seven membered ring. An attack of the secondary

oxygen will probably lead to the six membered ring, which is favored over the highly strained four membered ring.

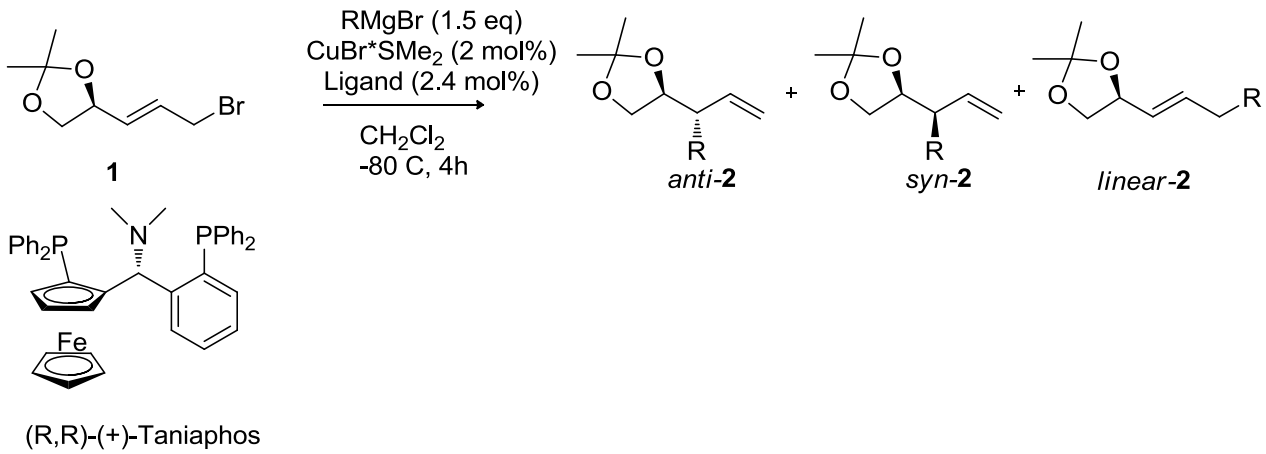
Results and discussion

The allylic bromide was first prepared in a three step synthesis from commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol as reported in literature in good to moderate yields. (Scheme 9)[6,7]



Scheme 9: Synthesis of the allyl bromide precursor.

The allylic alkylation was performed with two different Grignard reagents: EthylMgBr and HexylMgBr and with the two different enantiomers of the ligand Taniaphos. (Scheme 10, table 1)



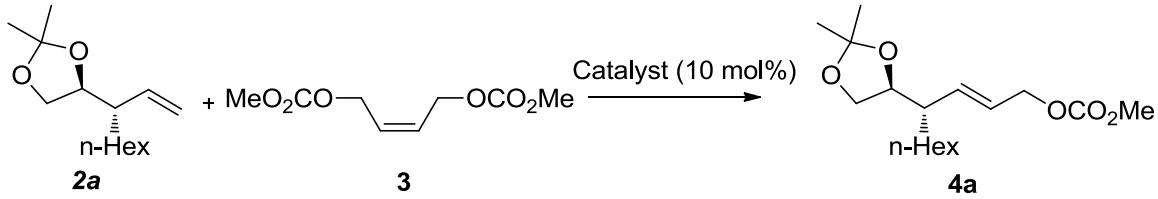
Scheme 10: Allylic alkylation of bromide **1** (top) and structure of the (R,R)-(+)-Taniaphos ligand.

Entry	R	Ligand	Anti %[a,b]	Syn %	Linear %
1	Hexyl (**2a**)	(+)-Taniaphos	100 (86)	0	0
2	Hexyl (**2b**)	(-)-Taniaphos	- (35)	- (22)	-
3	Ethyl (**2c**)	(+)-Taniaphos	93	5	2

Table 1: Product distributions of the allylic alkylations shown in scheme 8. (a) Product distribution determined by GC-MS. (b) Isolated yields shown in brackets.

Entry 1 shows total selectivity for the *anti*-hexyl-substituted product, as reported in literature. The exact product distribution in entry 2 was not determined. The isolated yields however show a very low

selectivity, which is most likely due to temperature. In literature is reported that an increase of only 5°C can shift the product distribution from 11:89:0 to 1:1:1.
The same problem occurred in entry 3, where a total selectivity for the *anti*-product is reported. The yield was not determined as the product was not fully dried as it might be volatile.



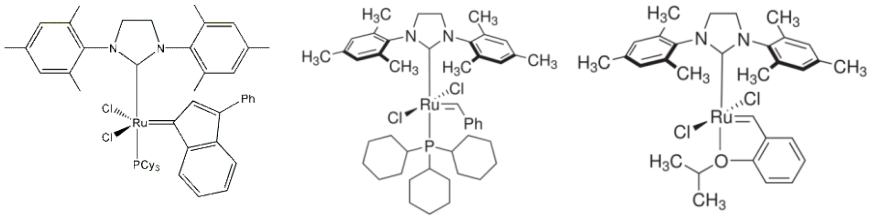
2a **3** **4a**

Scheme 11: Cross-metathesis of **2a** with dicarbonate **3** using a (Ru-based) catalyst.

4a was synthesized by cross-metathesis of **2a** with dicarbonate **3** using a Ruthenium catalyst. For this reaction, different catalyst and conditions were studied to optimize yields. (Table 2) For all catalysts, the best results were obtained using Toluene at 70°C. Highest yield was obtained using the Hoveyda-Grubbs 2nd gen. catalyst in toluene, achieving 79% yield.

Catalyst	Conditions[a]	Yield (%)
M-2	DCM, reflux	n.d. (conv <10%)[b]
	Toluene, 70°C	35
Grubbs 2nd gen	DCM, reflux	n.d. (conv 41%)
	Toluene, 70°C	42
Hoveyda-Grubbs 2nd gen	DCM, reflux	27
	Toluene, 70°C	79

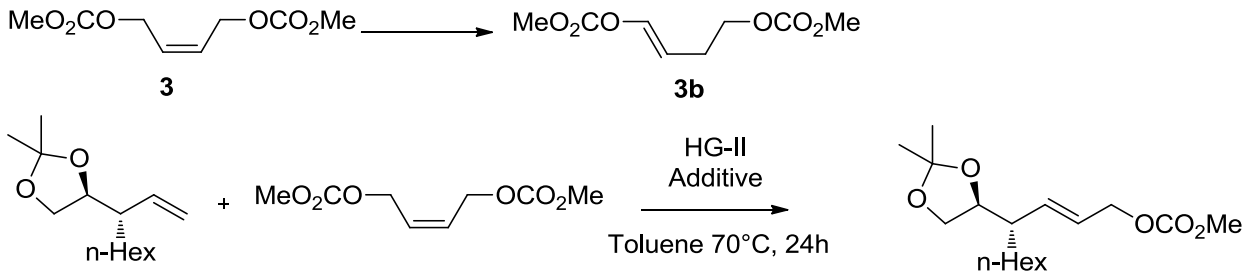
Table 2: Screening of various catalyst and conditions for the cross-metathesis shown in scheme 9. (a) *Reagents and conditions:* 0.1 M substrate, Catalyst (10 mol%), dicarbonate (2 eq.), 24h. (b) Conversion determined by GC-MS



C1 **C2** **C3**

Scheme 12: Structures of the used catalyst in the cross-metathesis. **C1**: M-2, **C2**: Grubbs 2nd gen, **C3**: Hoveyda-Grubbs 2nd gen.

A side product was observed during the cross-metathesis. The dicarbonate underwent isomerization to give product **3b**, giving rise to lower yields. This impurity was also difficult to remove by column chromatography. This isomerization during olefin metathesis is known and is caused by decomposition of the catalyst. It has been proposed that when the catalyst decomposes, it forms a Ruthenium hydride species, which can catalyze migration of the olefin. The reaction was also carried out using benzoquinones as additives, as it is known that these compounds prevent the isomerization.[8] (Scheme 13, Table 3)

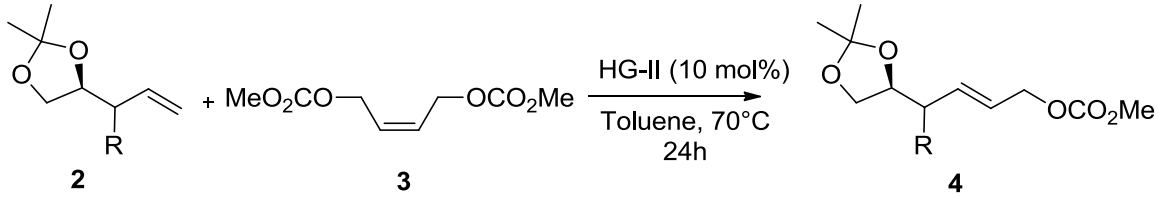


Scheme 13: Top: Isomerization of the dicarbonate. Bottom: Cross-metathesis carried out using benzoquinones as additives to prevent the abovementioned isomerization.

Entry[a]	Additive	Catalyst	Yield (%)	Conversion (%)[b]
1	Benzoquinone (10 mol%)	HG-II (5 mol%)	46	62
2	2,6-dichlorobenzoquinone (10 mol%)	HG-II (5 mol%)	n.d.	23
3	2,6-dichlorobenzoquinone (20 mol%)	HG-II (10 mol%)	29	29

Table 3: Cross-metathesis reaction shown in Scheme 13, using benzoquinone additives. (a) *Reagents and conditions:* 0.1 M substrate, dicarbonate **3** (2 eq.), Hoveyda-Grubbs 2nd gen. catalyst, Toluene, 70°C, 24h. (b) Determined with GC-MS.

When benzoquinone is used as an additive, a moderate yield was obtained, while using low catalyst loading (entry 1). The additive did not fully prevent the undesired isomerization, as side product **3b** was still observed. Next to this, benzoquinone showed to be difficult to remove by column chromatography. Therefore, the reaction was also carried out using 2,6-dichlorobenzoquinone. At low catalyst loading (entry 2), low conversion was observed. At higher catalyst loading (entry 3), a low yield was still obtained. And again, isomerization product **3b** was observed. The used benzoquinones seem to be unable to prevent the isomerization. Further study on this side reaction and used additives is needed.



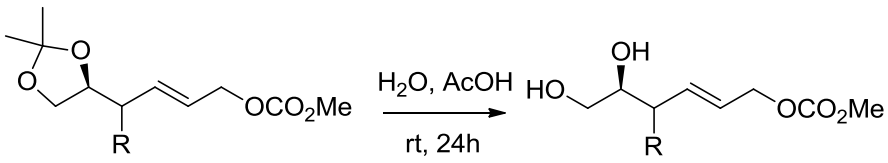
Scheme 14: Cross metathesis reaction of compound **2** with dicarbonate **3** to form carbonate **4**.

Entry[a]	R	Yield (%)
1	*anti*-hexyl (**4a**)	79
2	*syn*-hexyl (**4b**)	22
3[b]	*anti*-ethyl (**4c**)	n.d.[c]

Table 4: Cross-metathesis reaction shown in Scheme 14, with different alkyl substituents. (a) *Reagents and conditions*: 0.1 M substrate, dicarbonate **3** (2 eq.), Hoveyda-Grubbs 2nd gen. catalyst (10 mol%), Toluene, 70°C, 24h. (b) 5 mol% catalyst loading used, with additional 2 mol% after 16h. (c) Unable to separate product from dicarbonate side product **3b**, therefore yield could not be determined.

Table 4 shows the results of the cross-metathesis reaction carried out with different alkyl substituents. Entry 2 shows low yield for the cross-metathesis of the *syn*-hexyl substituted compound **2b**. Although the yield is not determined for entry 3, GC-MS analysis does indicate low conversion. The reason for these low yields might be the isomerization of the starting material as shown in scheme 13.

Product **4** was then deprotected under acidic conditions yielding diol **5** in good yields. (Scheme 14)



4 **5**

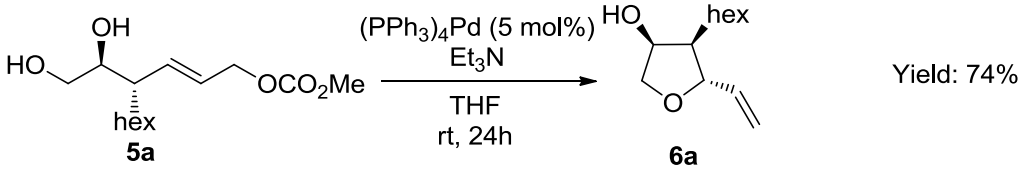
Scheme 15: Deprotection of product **4** to obtain diol **5**.

Entry	R	Yield (%)
1	*anti*-hexyl (**5a**)	99
2	*syn*-hexyl (**5b**)	89
3	*anti*-ethyl (**5c**)	n.d.[a]

Table 5: Deprotection of compounds **4** (Scheme 15). (a) Starting material was a mixture of *anti*-ethyl substituted carbonate **4c** and dicarbonate side product **3b**.

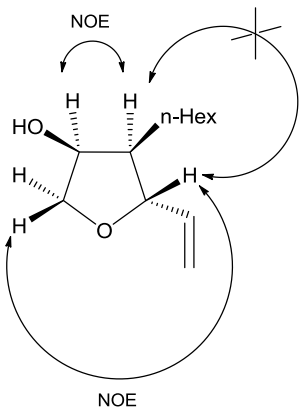
The yield of the reaction described in entry 3 was determined as the starting material **4c** still contained some dicarbonate impurities. The yield over 3 steps (allylic alkylation, cross-metathesis and deprotection) is 6%. The low yield is most likely due to the second step, the cross-metathesis.

The final step is the allylic etherification, creating the third stereocenter. This was carried out under basic conditions, using tetrakis(triphenylphosphine)palladium(0) as a (non chiral) catalyst. Remarkably, this reaction showed total regio- and diastereoselectivity for diol **5a**, giving rise to furan **6a**. (Scheme 16) Only one diastereomer was observed. The relative configuration was determined using dimensional NMR (COSY, NOESY). (Scheme 17) Cross peaks can be seen between the two protons which are next to the alcohol and the hexyl chain. Also, cross peaks can be seen between the protons next to the double bond substituent and the CH_2. On the contrary no cross peak can be seen between the protons next to the hexyl chain and the double bond substituent. As stated before, the only product that is observed is furan **6a**. Thus, the primary oxygen is more reactive than the secondary oxygen, as the four and six membered rings are not observed.



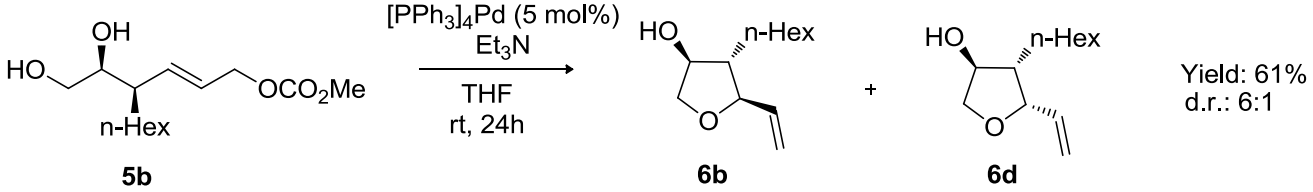
5a **6a**

Scheme 16: Intramolecular allylic etherification of diol **5a**.



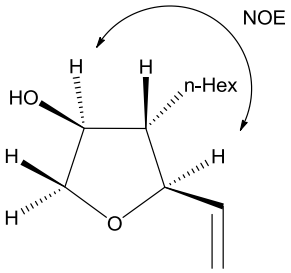
Scheme 17: Observed NOE between protons in furan **6a**

To test the hypothesis that the alkyl chain is directing the Palladium complex to obtain total diastereoselecitivy, the allylic etherification was also carried out starting from *syn*-hexyl substituted diol **5b** (Scheme 18). Expected is that the allyl substituent is *anti,* relative to the hexyl chain giving rise to furan **6b**. The NOESY spectrum showed that this is indeed the obtained configuration,(Scheme 19) as a cross peak can be seen between the protons next to the alcohol and the double bond substituent. In contrast to the etherification of **5a**, this reaction was not completely diastereoselective. Diastereomer **6d** is also observed. The diastereomeric ratio of **6b** to **6d** is 6:1. The reaction however did show total regioselectivity.



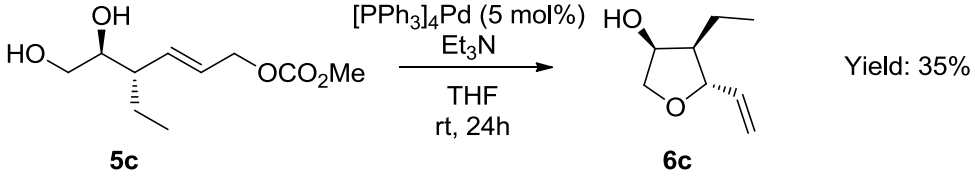
5b **6b** **6d**

Scheme 18: Intramolecular allylic etherification of diol **5b**. Diastereomeric ratio is based on ^{1}H-NMR. Configuration determined using NOESY NMR.



Scheme 19: Observed NOE in furan **6b**.

Finally, furan **6c** was synthesized starting from diol **5c** with total regio- and diastereoselectivity (Scheme 20). A low yield is here obtained, probably due to the fact that furan **6c** is probably volatile. The configuration is expected to be consistent with furan **6a**. This is confirmed by similar ^{1}H-NMR patterns.



5c **6c**

Scheme 20: Intramolecular allylic etherification of diol **5c**.

Future plans

Future work could include broadening the scope of this reaction by altering the alkyl chain.
Next to this, the selectivity in the allylic etherification should be further studied, starting with the analysis of furan **6b**. Chiral ligands might also be used to control stereochemistry.
Also, the cross-metathesis reaction can be further optimized.

Conclusion

In summary, an enantioselective protocol to highly substituted chiral furans has been developed, based on a Cu-catalyzed asymmetric allylic alkylation, a cross metathesis and a ring closing etherification which was performed with total regio- and stereocontrol. Also, the cross-metathesis for this route is studied to improve yields.

Experimental

(*S,E*)-Methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate

The procedure was followed as described in literature.[6] A slurry of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (2.62 g, 10 mmol) in 20 ml 5% aqueous $NaHCO_3$ was stirred at 0°C. A solution of $NaIO_4$ (2.63 g, 12.3 mmol) in 20 ml H_2O was added dropwise. The solution was stirred for 1h at room temperature. The solution was cooled to 0°C and triethyl-α- phosphonoacetate (9.35 g, 41.7 mmol) was added with 62.5 ml of a 6 M K_2CO_3 solution. The solution was stirred for 24h at room temperature.
The mixture was extracted with CH_2Cl_2, dried with $MgSO_4$, filtered and concentrated to obtain a yellow oil. Which was purified with column chromatography (SiO_2, pentane/ether 5:1) to obtain 2.49 g (14.5 mmol, 72%) of the (*E*)-ester and 0.173 g (1.00 mmol, 5%) of the (*Z*)-ester.
^{1}H NMR (200 MHz, $CDCl_3$) δ 6.88 (dd, J = 15.6, 5.6, 1H), 6.10 (dd, J = 15.6, 1.4, 1H), 4.73 – 4.60 (m, 1H), 4.28 – 4.12 (m, 1H), 3.68 (dd, J = 8.2, 7.1, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.29 (t, J = 7.1, 3H).

(*S,E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol

The procedure was followed as described in literature.[6] 36.3 ml of DIBAH (1 M in dichloromethane) was added dropwise to a solution of (*E*)-ester (2.49 g, 14.5 mmol) in dry CH_2Cl_2 at -78°C. The solution was stirred 2h at -78°C. 22 ml of ether and 2.9 ml water were added and the mixture was allowed to warm to room temperature, and a white gel formed. 2.2 ml H_2O and 4.0 ml 4M NaOH were added and a white precipitate formed. The mixture was dried with Na_2SO_4, filtered and the solvents were removed to obtain 2.21 g (14.0 mmol, 96%) of the alcohol without further purification.
^{1}H NMR (200 MHz, $CDCl_3$) δ 5.94 (dt, J = 15.5, 5.0, 1H), 5.69 (ddt, J = 1.4, 7.4, 15.4 Hz, 1H), 4.52 (dd, J = 13.9, 7.2, 1H), 4.10 (m, 3H), 3.58 (t, J = 7.9, 1H), 1.85 (bs, 1H), 1.41 (s, 1H), 1.37 (s, 1H).

(*S,E*)-4-(3-Bromoprop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolane (1)

The procedure was followed as described in literature.[7] Triphenylphospine (4.039 g, 15.4 mmol) was added to a solution of alcohol (2.214 g, 14.0 mmol) in 88 ml CH_2Cl_2. NBS (2.670 g, 15.0 mmol) was slowly added in portions and the mixture was stirred 3h at room temperature. The mixture was washed with water and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated to a yellow liquid. The liquid was taken up in pentane/ether (1:1), the yellow precipitate was filtered and the filtrate was concentrated. This was repeated 4 times. After purification with column chromatography (SiO_2, pentane/ether 3:1) 1.866 g (8.4 mmol, 60%) of bromide **1** was obtained.
^{1}H NMR (200 MHz, $CDCl_3$) δ 6.07 – 5.89 (m, 1H), 5.73 (dd, J = 15.2, 7.0, 1H), 4.50 (q, J = 6.9, 1H), 4.08 (dd, J = 8.2, 6.3, 1H), 3.92 (d, J = 7.4, 2H), 3.58 (dd, J = 8.2, 7.5, 1H), 1.40 (s, 3H), 1.36 (s, 3H).
^{1}H-NMR data is in accordance with literature.[7]

(*S*)-2,2-Dimethyl-4-((*R*)-non-1-en-3-yl)-1,3-dioxolane (2a)

The procedure was followed as described in literature.[1] $CuBr{\cdot}SMe_2$ (10,3 mg, 50 µmol) and (+)-Taniaphos (41.2 mg, 60 µmol) were dissolved in 20 ml CH_2Cl_2 and stirred for 15 minutes. The mixture was cooled to -80°C and 3.75 ml hexyl magnesium bromide (2 M in Et_2O, 1.5 eq) was added dropwise. Bromide **1** (1.105 g, 5 mmol) was dissolved in 8 ml CH_2Cl_2 and added over 1h. The mixture was stirred overnight at -80°C. The reaction was then quenched with 5 ml methanol and allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (20 ml) was added and the aqueous layers were extracted with

Et_2O. The combined organic layers were dried with Na_2SO_4, filtered and concentrated. 0.97 g (4.29 mmol, 86%) of **2a** was obtained after purification with column chromatography (SiO_2, pentane/ether 30:1).
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.65 (dt, J = 17.0, 10.3, 1H), 5.13 (dd, J = 10.4, 2.0, 1H), 5.04 (ddd, J = 17.1, 2.1, 0.6, 1H), 4.10 – 3.93 (m, 2H), 3.71 – 3.56 (m, 1H), 2.16 – 2.00 (m, 1H), 1.39 (s, 1H), 1.34 (s, 1H), 1.45 – 1.11 (m, 10H), 0.87 (t, J = 6.1, 1H).
^{1}H-NMR data is in accordance with literature.[1]

(*S*)-2,2-Dimethyl-4-((*S*)-non-1-en-3-yl)-1,3-dioxolane (2b)
The procedure was followed as described in literature.[1] CuBr·SMe_2 (4.11 mg, 20 µmol) and (-)-Taniaphos (16.5 mg, 24 µmol) were dissolved in 4 ml CH_2Cl_2 and stirred for 15 minutes. The mixture was cooled to -80°C and 0.75 ml hexyl magnesium bromide (2 M in Et_2O, 1.5 eq) was added dropwise. Bromide **1** (221 mg, 1 mmol) was dissolved in 1.6 ml CH_2Cl_2 and added over 1h. The mixture was stirred overnight at -80°C. The reaction was then quenched with 1 ml methanol and allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (4 ml) was added and the aqueous layers were extracted with Et_2O. The combined organic layers were dried with Na_2SO_4, filtered and concentrated. 49.6 mg (0.219 mmol, 22%) of **2b** and 79 mg (0.349 mmol, 35%) of **2a** were obtained after purification with column chromatography (SiO_2, pentane/ether 30:1).
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 – 5.44 (m, 1H), 5.10 – 5.03 (m, 2H), 3.95 – 3.87 (m, 2H), 3.66 – 3.59 (m, 1H), 2.17 – 2.07 (m, 1H), 1.69 (dt, J = 7.4, 4.7, 1H), 1.40 (s, 3H), 1.41 – 1.12 (m, 9H), 1.35 (s, 3H), 0.87 (t, J = 6.8, 3H).
^{1}H-NMR data is in accordance with literature.[1]

(*S*)-2,2-Dimethyl-4-((*S*)-pent-1-en-3-yl)-1,3-dioxolane (2c)
The procedure was followed as described in literature.[1] CuBr·SMe_2 (4.11 mg, 20 µmol) and (+)-Taniaphos (16.5 mg, 24 µmol) were dissolved in 4 ml CH_2Cl_2 and stirred for 15 minutes. The mixture was cooled to -80°C and 0.5 ml ethyl magnesium bromide (3 M in Et_2O, 1.5 eq) was added dropwise. Bromide **1** (221 mg, 1 mmol) was dissolved in 1.6 ml CH_2Cl_2 and added over 1h. The mixture was stirred overnight at -80°C. The reaction was then quenched with 1 ml methanol and allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (4 ml) was added and the aqueous layers were extracted with Et_2O. The combined organic layers were dried with Na_2SO_4, filtered and concentrated. The product was purified with column chromatography (SiO_2, pentane/ether 30:1).
^{1}H-NMR data is in accordance with literature.[1]

(*S,E*)-4-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)dec-2-en-1-yl methyl carbonate (4a)
Hoveyda-Grubbs 2nd gen catalyst (8.30 mg, 13.25 µmol, 10 mol%) was dissolved in 1.3 ml dry degassed toluene. **2a** (30 mg, 0.133 mmol) and dicarbonate **3** (54.1 mg, 0.265 mmol, 2 eq.) were added and the mixture was stirred at 70°C for 21h. Purification with column chromatography (SiO_2, pentane/ether 4:1) afforded 33 mg (0.105 mmol, 79%) of carbonate **4a**.
$[\alpha]_D^{20}$ = +20.0 (c = 1.0 in $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.63 (m, 2H), 4.64 – 4.58 (m, 2H), 4.01 (m, 2H), 3.78 (s, 3H), 3.66 – 3.54 (m, 1H), 2.21 – 2.07 (m, 1H), 1.38 (s, 3H), 1.33 (s, 3H), 1.41 – 1.13 (m, 10H), 0.87 (t, J = 6.8, 3H).
^{13}C NMR (50 MHz, $CDCl_3$): δ 159.0, 136.2, 125.6, 108.8, 78.3, 68.4, 67.4, 54.7, 45.6, 31.7, 30.9, 29.2, 27.0, 26.4, 25.4, 22.6, 14.0

(*R,E*)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)dec-2-en-1-yl methyl carbonate (4b)
Hoveyda-Grubbs 2nd gen catalyst (6.52 mg, 0.0104 mmol, 5 mol%) was dissolved in 2 ml dry degassed toluene. **2b** (47 mg, 0.208 mmol) and dicarbonate **3** (84.9 mg, 0.416 mmol, 2 eq) were added and the

mixture was stirred at 70°C for 24h. Purification with column chromatography (SiO_2, pentane/ether 4:1) affored 14.2 mg (0.0452, 22%) of carbonate **4b**
$[\alpha]_D^{20}$= +0.8 (c = 1.0 in $CHCl_3$)
^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.64 (dt, J = 15.5, 6.1, 1H), 5.52 (dd, J = 15.5, 9.0, 1H), 4.58 (d, J = 6.1, 2H), 3.98 – 3.87 (m, 2H), 3.78 (s, 3H), 2.21 – 2.13 (m), 1.72 – 1.61 (m, 1H), 1.39 (s, 1H), 1.34 (s, 1H), 1.36 – 1.11 (m, 9H), 0.87 (t, J = 6.9, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.0, 136.3, 126.3, 109.4, 78.7, 68.6, 68.1, 55.2, 47.2, 32.2, 31.4, 29.7, 27.3, 27.2, 26.0, 23.0, 14.5

(*S,E*)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-2-en-1-yl methyl carbonate (4c)
Hoveyda-Grubbs 2nd gen catalyst (31.33 mg, 0.05 mmol) was dissolved in 10 ml dry degassed toluene. The product of the allylic alkylation (**2c**) was added directly without fully removing all solvents. Dicarbonate **3** (408 mg, 2 mmol) was added and the mixture was stirred for 24h at 70°C. After 16h, 2 mol% of Hoveyda-Grubbs 2nd gen catalyst was added (12.53 mg, 0.02 mmol). Purification with column chromatography (SiO_2, pentane/ether 3:1) afforded 51.5 mg of a mixture of carbonate **4c** and dicarbonate **3b**.

(*S,E*)-4-((*S*)-1,2-Dihydroxyethyl)dec-2-en-1-yl methyl carbonate (5a)
Carbonate **4** (40.3 mg, 0.128 mmol) was dissolved in 0.27 ml H_2O and 0.67 ml AcOH and stirred at room temperature for 24h. After 4 coevaporations with toluene, 34.8 mg (0.127 mmol, 99%) of diol **5** was obtained without further purification.
$[\alpha]_D^{20}$= +10.8 (c = 1.0 in $CHCl_3$)
^{1}H NMR (200 MHz, $CDCl_3$): δ 5.70 – 5.62 (m, 2H), 4.61 (d, J = 4.9, 2H), 3.78 (s, 3H), 3.73 – 3.45 (m, 3H), 2.22 – 2.04 (m, 1H), 2.08 (s, 1H), 1.54 – 1.37 (m, 1H), 1.41 – 1.10 (s, 10H), 0.87 (t, J = 6.4, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 136.4, 126.4, 73.9, 68.2, 64.9, 54.8, 45.9, 31.7, 30.8, 29.2, 27.1, 22.6, 14.0

(*R,E*)-4-((*S*)-1,2-dihydroxyethyl)dec-2-en-1-yl methyl carbonate (5b)
Carbonate **4b** (17.7 mg, 0.0563 mmol) was dissolved in 0.11 ml H_2O and 0.26 ml AcOH and stirred for 24h. After 4 coevaporations with toluene, 13.8 mg of diol **5b** (0.0503 mmol, 89%) was obtained without further purification.
$[\alpha]_D^{20}$= +5.0 (c = 1.0 in $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 – 5.47 (m, 2H), 4.59 (d, J = 5.8, 2H), 3.78 (s, 3H), 3.66 (dd, J = 10.9, 2.5, 1H), 3.56 (td, J = 7.5, 2.8, 1H), 3.45 (dd, J = 10.9, 7.6, 1H), 2.24 – 2.11 (m, 1H), 1.70 – 1.58 (m, 1H), 1.35 – 1.08 (m, 9H), 0.87 (t, J = 6.7, 3H).
^{13}C NMR (200 MHz, $CDCl_3$) δ 155.6, 136.2, 125.9, 74.3, 68.1, 64.8, 54.8, 46.5, 31.7, 30.4, 29.3, 27.0, 22.6, 14.0
HRMS (APCI+, m/z): calculated for $C_{14}H_{26}O_5$ [M+H$^+$]: 275.1853, found: 275.1405

(*4S,5S,E*)-4-ethyl-5,6-dihydroxyhex-2-en-1-yl methyl carbonate (5c)
The mixture of carbonate **4c** and dicarbonate **3b** (50.4 mg) is dissolved in 0.39 ml H_2O and 0.98 ml AcOH and stirred 24h at room temperature. After column chromatography (SiO_2, pentane/ether 1:1 to obtain dicarbonate, pure ether to obtain product), diol **5c** (13.7 mg, 0.0628 mmol 6% over 3 steps) is obtained.
$[\alpha]_D^{20}$= +12.4 (c = 1.0)
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 – 5.58 (m, 2H), 4.67 – 4.54 (m, 2H), 3.78 (s, 3H), 3.69 – 3.58 (m, 2H), 3.52 (dd, J = 10.7, 6.9, 1H), 1.60 – 1.49 (m, 1H), 1.39 – 1.17 (m, 2H), 0.90 – 0.82 (m, 3H).
^{13}C NMR (200 MHz, $CDCl_3$) δ 155.6, 136.1, 126.7, 73.6, 68.2, 64.9, 54.8, 47.6, 23.7, 11.7

(*3S,4R,5S*)-4-Pentyl-5-vinyltetrahydrofuran-3-ol (6a)
Tetrakis(triphenylphospine)palladium (4.2 mg, 3.6 µmol) was dissolved in 0.2 ml THF. Diol **5a** (23 mg, 0.073 mmol) and a drop of triethylamine were added and the mixture was stirred for 24h at room temperature. 2 mL water was added and extracted with ether. The combined layers were dried over Na_2SO_4 and concentrated. After column chromatography (SiO_2, pentane/ether 1:1) furan **6a** (10.7 mg, 0.054 mmol, 74%) was obtained.
$[\alpha]_D^{20}$= - 42.6 (c = 1.0 in $CHCl_3$)
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.4, 10.1, 7.4, 1H), 5.22 (dd, J = 30.8, 13.6, 2H), 4.35 (t, J = 3.7, 1H), 4.10 – 3.98 (m, 2H), 3.83 (d, J = 10.0, 1H), 1.79 – 1.66 (m, 1H), 1.41 – 1.18 (m, 10H), 0.87 (t, J = 6.5, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 117.0, 83.7, 75.5, 73.1, 50.6, 31.7, 29.5, 28.0, 24.6, 22.6, 14.1
HRMS (ESI+, m/z): calculated for $C_{12}H_{22}O_2$ [M+H$^+$]: 199.1693, found: 199.1691

4-hexyl-5-vinyltetrahydrofuran-3-ol (6b)
Tetrakis(triphenylphospine)palladium (2.0 mg, 1.8 µmol) was dissolved in 0.2 ml THF. Diol **5b** (11 mg, 0.0350 mmol) and a drop of triethylamine were added and the mixture was stirred for 24h at room temperature. 2 mL water was added and extracted with ether. The combined layers were dried over Na_2SO_4 and concentrated. After column chromatography (SiO_2, pentane/ether 1:1) furan **6b** (4.2 mg, 0.0212 mmol, 61%) was obtained.
$[\alpha]_D^{20}$= - 13.3 (c = 0.42 in $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddd, J = 17.2, 10.5, 6.7, 1H), 5.29 (dt, J = 17.2, 1.5, 1H), 5.19 (dt, J = 15.7, 3.4, 1H), 4.60 (t, J = 6.4, 1H), 4.22 (dt, J = 6.1, 3.2, 1H), 4.12 (dd, J = 9.7, 5.2, 1H), 3.66 (dd, J = 9.6, 3.1, 1H), 2.09 – 1.98 (m, 1H), 1.43 – 1.06 (m, 10H), 0.88 (t, J = 6.8, 3H).
^{13}C NMR (200 MHz, $CDCl_3$) δ 135.2, 116.8, 81.7, 76.7, 73.8, 51.5, 31.7, 29.5, 28.0, 27.2, 22.6, 14.0

(3S,4R,5S)-4-ethyl-5-vinyltetrahydrofuran-3-ol (6c)
Tetrakis(triphenylphospine)palladium (3.6 mg, 3.11 µmol) was dissolved in 0.2 ml THF. Diol **5c** (11.4 mg, 0.0522 mmol) and a drop of triethylamine were added and the mixture was stirred for 24h at room temperature. 2 mL water was added and extracted with ether. The combined layers were dried over Na_2SO_4 and concentrated. After column chromatography (SiO_2, pentane/ether 1:1) furan **6c** (2.6 mg, 0.0183 mmol, 35%) was obtained.
[α] = -67.1 (c = 0.14 in $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, J = 17.2, 10.2, 7.3, 1H), 5.33 – 5.22 (m, 1H), 5.21 – 5.12 (m, 1H), 4.38 (t, J = 4.0, 1H), 4.09 – 4.00 (m, 2H), 3.84 (d, J = 10.0, 1H), 1.67 (ddd, J = 14.3, 9.6, 4.5, 1H), 1.57 – 1.36 (m, 2H), 1.01 (t, J = 7.4, 3H).
^{13}C NMR (200 MHz, $CDCl_3$) δ 138.1, 116.9, 83.6, 75.5, 72.9, 52.4, 17.7, 12.6

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