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Synthesis of Dihydrofurans and Dihydropyrans with Unsaturated Side Chains Based on Ring Size-Selective Ring-Closing Metathesis

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Dedicated to Prof. Philip J. Kocieński on the occasion of his 60th birthday.

Abstract: Enantiomerically pure 1,5-hexadiene-3,4-diol, derived from D-mannitol in a few steps, may serve as a starting material for enantiopure dihydropyrans and dihydrofurans bearing an unsaturated side chain which is amenable for further synthetic transformations. The synthesis relies on a ring size-selective ring-closing metathesis reaction of a triene. Most likely, a catalyst-directing effect of an allylic hydroxy group is responsible for the selectivity.

Keywords: dihydrofurans; dihydropyrans; metathesis; oxacycles; ruthenium

Introduction

Five- and six-membered oxacycles are ubiquitious structural motifs in a large number of natural and non-natural biologically active compounds, or serve as key intermediates in their synthesis.[1–5] The Annonaceous acetogenins, for instance, are prominent examples. They have attracted considerable interest over the past few decades due to their promising biological activities, such as antitumor or pesticidal activity.[6,7] Particularly important structural elements present in these compounds are tetrahydrofurans **I** bearing a side chain with an α-hydroxy group in the 2-position, and tetrahydropyrans **II** with a 2,3-arrangement of an alkyl side chain and a hydroxy group. Some examples also include an adjacent bis-THF moiety **III**. Figure 1 illustrates this point for the structures of the Annonaceous acetogenins goniotetracin, pyragonicin and bullacin.[7]

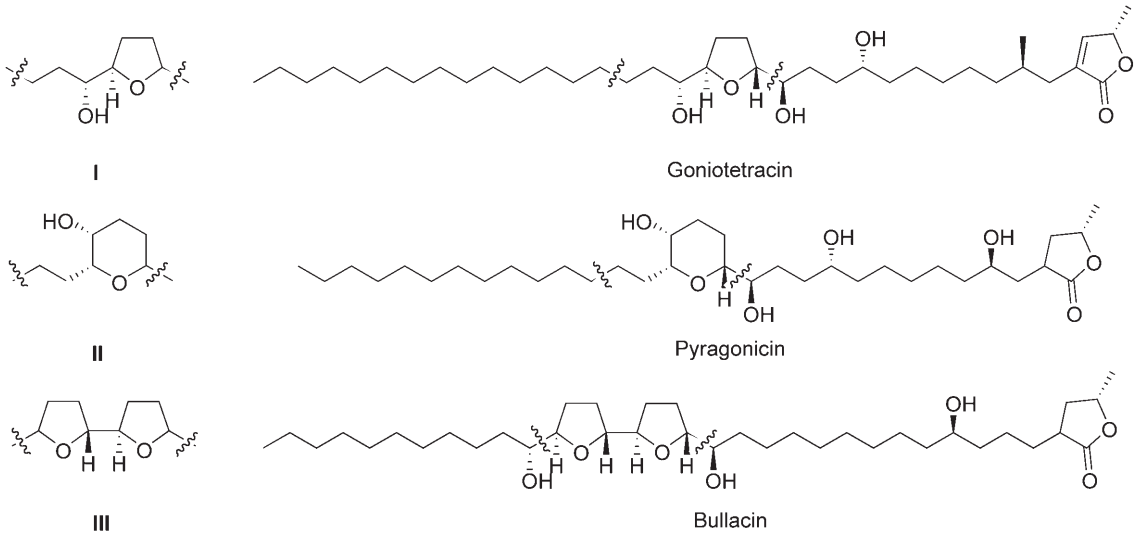
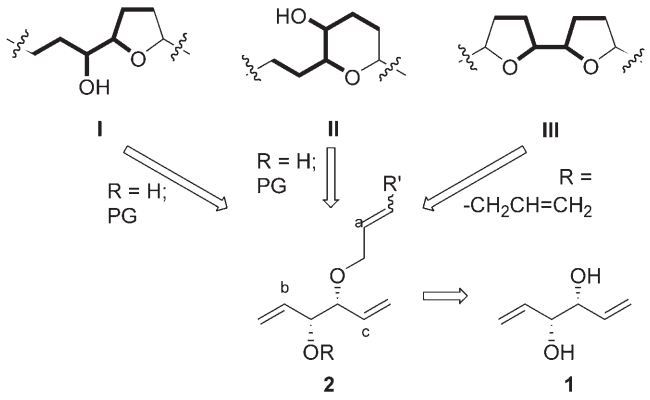


Figure 1. Structures of Annonaceous acetogenins with representative structural motifs.



Scheme 1. Common precursor for skeletons **I**–**III**.

It is an interesting feature of the structural motifs **I**–**III** that they display a common skeleton of carbon and oxygen atoms, which is highlighted in Scheme 1. In continuing previous works in our group dedicated to the exploitation of the olefin metathesis reaction[8–13] for the synthesis of functionalized oxacycles,[14–19] we wondered if the common arrangement of carbon and oxygen atoms in **I**, **II** and **III** could be accessed by a common precursor, hexadienediol **1**, after its transformation to tri- or tetraenes **2** (Scheme 1). This would be particularly attractive from the synthetic point of view, as **1** is easily available in multi-gram quantities from D-mannitol,[20,21] while its enantiomer *ent*-**1** can be synthesized from *R*,*R*-dimethyl tartrate.[22]

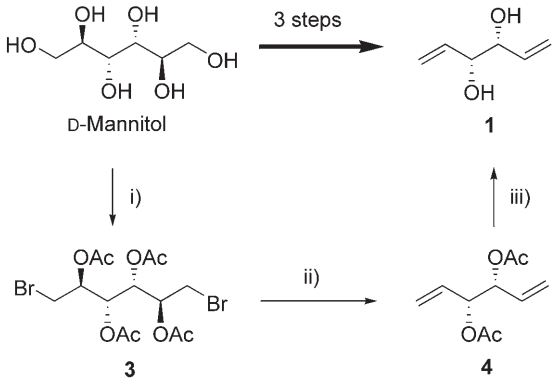
Both **1** and *ent*-**1** have previously been used as building blocks for the synthesis of metathesis precursors: for instance, Quinn et al. reported the total synthesis of the five-membered ring lactones muricatacin[23] and rollicosin[24] from **1**, while Michaelis and Blechert recently published a synthesis of the six-membered ring lactone phomopsolide C from *ent*-**1**.[22] Burke et al. exploited the C_2-symmetry of dienediol **1** in the total synthesis of several natural products, such as brevicomin,[25] sialic acids,[26] and densely functionalized spiroacetals.[27] Finally, Donohoe et al. used a mixture of racemic **1** and its *meso*-diastereomer, after acetalization with methoxyallene and double RCM of the resulting tetraene, as a precursor for bisfuran.[28] Obviously, like for many other tri-, tetra- or polyenes, the use of metathesis precursors derived from **1** in RCM reactions is associated with either stereo- or regioselectivity issues. This aspect of olefin metathesis has recently been reviewed by us.[29] Particularly relevant for the subject of this study are reports where different modes of cyclization result in different ring sizes,[30] such as the RCM-based synthesis of fused *vs.* "dumbbell"-type bicyclic lactams,[31,32] the strong preference for "dumbbell"-type oxacycles in the RCM of tetra-[33,34] or hexaenes.[35] Parallel to our preliminary account on the control of ring size-selectivity in RCM reactions of trienes **2**,[36] two reports by Crimmins et al. were published where the regioselective ring closure of structurally closely related trienes is described and efficiently used in the total syntheses of the Annonaceous acetogenin (−)-mucocin[37] and the microbial metabolite (+)-SCH 351448.[38] In this paper, we provide a full account of our studies dedicated to the selective construction of structural patterns **I**, **II** and **III** *via* regioselective RCM of tri- and tetraenes **2**.

Results and Discussion

Synthesis of Metathesis Precursors

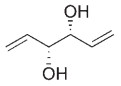
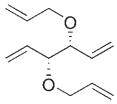
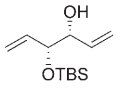
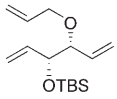
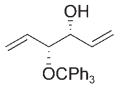
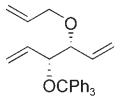
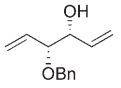
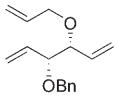
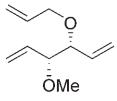
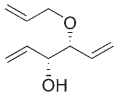
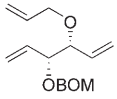
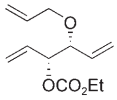
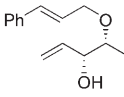
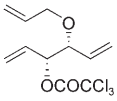
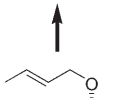
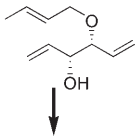
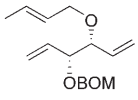
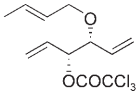
The common starting material for all metathesis precursors of general structure **2** was *R*,*R*-1,5-hexadiene-3,4-diol (**1**), which was synthesized from D-mannitol in three steps, following a slightly modified literature procedure.[20,21] To this end, D-mannitol was first treated with acetyl bromide, followed by acetylation of the remaining hydroxy groups to give **3**.[20] Compound **3** undergoes elimination of bromide and acetate under reducing conditions, as previously described by Burke et al.,[21] to give the diacetate **4**. Deacetylation of **4** was conducted as a separate step and achieved by methanolysis in the presence of a catalytic amount of aqueous K_2CO_3, rather than NaOMe. Thus, **1** becomes available from D-mannitol in three steps in multi-gram quantities in 35% overall yield (Scheme 2).

Starting from dienediol **1**, a set of metathesis precursors of the general structure **2** with various steric and electronic properties was prepared by various methods. In most cases, a selective functionalization of one OH group is required prior to modification of the second one. Table 1 and Scheme 3 provide an overview of the metathesis precursors employed in this study and the methods used for their preparation.

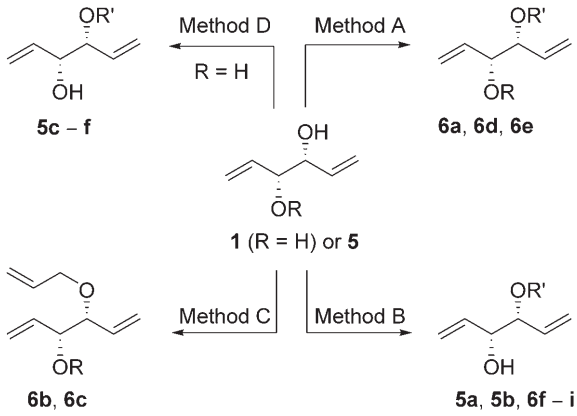


Scheme 2. *Reagents and conditions*: i) acetyl bromide, dioxane; then Ac_2O, pyridine (50%); ii) Zn, glacial acetic acid (85%); iii) MeOH, K_2CO_3 (aqueous) (86%).

Table 1. Yields of protected metathesis substrates **6a–j** (right half of table), their corresponding starting materials **1** and **5a–f** (left half of table), and the general method of synthesis (see Scheme 3).

Starting Material	No./Yield	Method	Product	No./Yield	Method
	**1** (see scheme 2)			**6a**/87%	A
	**5a**/75%	B		**6b**/74%	C
	**5b**/79%	B		**6c**/82%	C
	**5c**/65%	D		**6d**/97%	A
				**6e**/60%	A
	**5d**/85%	D		**6f**/69%	B
				**6g**/79%	B
	**5e**/43%	D		**6h**/23%	B
			--	--	--
	**5f**/88%	D		**6i**/71%	B
				**6j**/27%	B

Method A is a routine Williamson ether synthesis. This can only be used for the double allylation of tetraene **6a** and alkylation of alcohols **5c**,**d** where the first OH group has already been converted to a stable, non-migrating group. Method B is the selective introduction of one bulky protecting group under moderately basic conditions. Functionalization of the second OH group is unfavorable due to steric hindrance. Compounds **5a**[24] and **5b**[22] have previously been obtained *via* this method. Method C is a Pd-catalyzed *O*-allylation[39] which has proven useful in cases where a protecting group migration or rather low reactivity has to be expected. We used this



Scheme 3. *General reagents and conditions*: Method A: NaH, R′X, THF, 65 °C; Method B: R′X, imidazole or pyridine, DCM, 25 °C; Method C: allyl ethyl carbonate, $Pd(PPh_3)_4$, THF, 65 °C; Method D: "Bu_2SnO", benzene, R′X.

method for the synthesis of **6b**,**c** from **5a**,**b**. Selective mono-functionalization of **1** cannot be achieved by Williamson ether synthesis, as double etherification will inevitably occur under these conditions. Therefore, method D was used which proceeds *via* the intermediate formation of a stannylene diacetal of **1**, which is subsequently cleaved with an appropriate alkylating agent. This method, which had originally been developed for selective manipulation of OH groups in carbohydrates,[40] has previously been used for the preparation of **5c**.[23] Scheme 3 summarizes the four synthetic methods used to convert **1** into the metathesis precursors **5** and **6** in one or two steps, respectively.

Regioselective Double RCM: Fused *vs.* Dumbbell-Type Bicyclic Structures

A considerable number of ruthenium-based metathesis precatalysts has been described in the literature.[9,10] Figure 2 shows the structures of the first-generation ruthenium precatalysts **A**[41] and **B**[42] and the second-generation precatalysts **C**,[43] **D** and **E**[44] which have been used in the course of this study.

Ring-closing metathesis of tetraene **6a** may result in the formation of four products: apart from the fused (**9**) and dumbbell-type bicyclic product (**10**) monocyclized dihydropyran **7a** and dihydrofuran **8a** have to be expected (Scheme 4 and Table 2). At the beginning, RCM of **6a** in the presence of 5 mol % **A** or **C**–**E**, respectively, was investigated at ambient temperature under otherwise identical conditions.

Surprisingly, a small amount of monocyclized products **7a** and **8a** could be detected with phosphine-free catalysts **D** and **E** (entries 3 and 4) while **A** and **C** (normally considered to be less active) lead to the exclusive formation of bicyclic products **9** and **10**. With

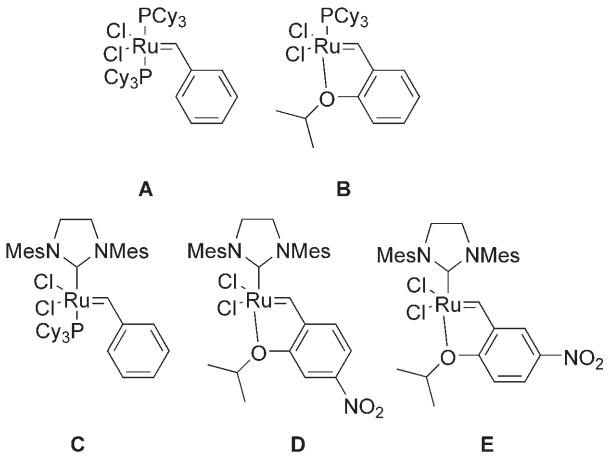
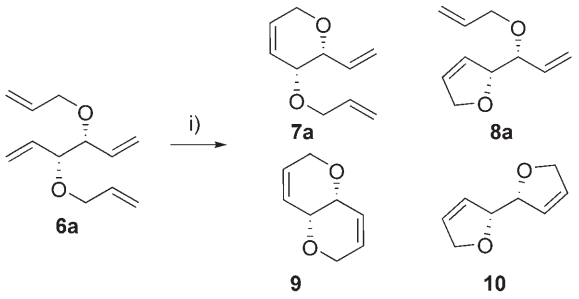


Figure 2. Ruthenium precatalysts used in this study.



Scheme 4. *General reagents and conditions*: i) catalyst (5 mol%), (for details with respect to solvent, temperature and pressure see Table 2).

first generation catalyst **A** the reaction is highly selective, giving exclusively the bis-dihydrofuran **10** (^{1}H NMR, entry 1), whereas **C** results in the formation of fused (**9**) and dumbbell-type product (**10**) in a ratio of 1.0:1.7 (entry 2). Both bicyclic products could be isolated and were characterized by one- and two-dimensional NMR spectroscopy. The structural assignment is based on the value for the vicinal coupling constant ^3J(−HC=CH−), which is 10.2 Hz for **9** and 6.3 Hz for **10**, with both values being typical for dihydropyrans and dihydrofurans, respectively.[19] Another distinctive feature is the chemical shift value of the ether carbon atoms (**9**: 67.8 and 65.4 ppm; **10**: 88.0 and 75.8 ppm). These values are also in the normal range for dihydropyrans or dihydrofurans, respectively.[19] Apart from the incomplete conversion observed for catalysts **D** and **E**, the ratio of bicyclic products **9** and **10** is comparable to that observed for **C** (Table 2, entries 1–4). Given the high selectivity obtained with the least reactive catalyst **A**, one might speculate that kinetic control is the origin of the perfect ring size-selectivity. Consequently, the ring-closing metathesis of **6a** was repeated in refluxing toluene. Under these conditions all catalysts give full conversion to bicyclic products **9** and **10** and the amount of six-membered product **9** increases slightly (Table 2, entries 5–8). If there is indeed a thermodynamic preference for the fused six-membered ring product **9**, it should be possible to promote its formation by conducting the reaction under an atmosphere of ethylene. This might facilitate a ring-opening metathesis of the kinetic product and eventually result in a larger quantity of **9**. To check this possibility, all four experiments were repeated in toluene at 110 °C under an atmosphere of

Table 2. Ring size-selective double RCM of **6a**. Conditions and product ratios.

Entry	Solvent	T [°C]	Catalyst (5 mol%)	P [bar]	Conversion [%]	Product Ratio [**9**:**10**:(**7a**+**8a**)][a]
1	CH_2Cl_2	20	**A**	1 (Ar)	99	only **10**[b]
2	CH_2Cl_2	20	**C**	1 (Ar)	99	1.0:1.7:0
3	CH_2Cl_2	20	**D**	1 (Ar)	90	1.0:1.9:0.6
4	CH_2Cl_2	20	**E**	1 (Ar)	90	1.0:1.8:0.4
5	toluene	110	**A**	1 (Ar)	99	1.0:11.0:0
6	toluene	110	**C**	1 (Ar)	99	1.0:1.4:0
7	toluene	110	**D**	1 (Ar)	99	1.0:1.6:0
8	toluene	110	**E**	1 (Ar)	99	1.0:1.4:0
9	toluene	110	**A**	12 (C_2H_4)	99	1.0:8.0:0.2
10	toluene	110	**C**	12 (C_2H_4)	80	1.0:1.5:0.4
11	toluene	110	**D**	12 (C_2H_4)	85	1.0:0.8:0.2
12	toluene	110	**E**	12 (C_2H_4)	85	1.0:1.5:0.3
13	toluene	110	**A**	12 (C_2H_4), 30 (Ar)	95	1.0:5.0:0.3
14	toluene	110	**C**	12 (C_2H_4) 30 (Ar)	99	1.0:1.4:0
15	toluene	110	**D**	12 (C_2H_4), 30 (Ar)	90	1.0:1.4:0.2
16	toluene	110	**E**	12 (C_2H_4), 30 (Ar)	90	1.0 : 1.6 : 0.2

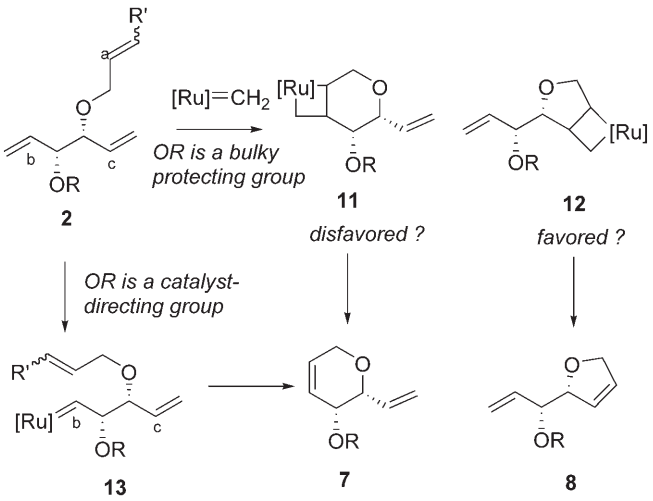
[a] Conversion and product ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[b] Isolated yield: 49%.

12 bars of ethylene. Not surprisingly, small amounts of monocyclic products are now observed for all catalysts (Table 2, entries 9–12). Remarkably, we observed for the first time that the six-membered ring product **9** is formed in a larger quantity than the five-membered product **10** (Table 2, entry 11) if precatalyst **D** is used. Finally, it was investigated whether the problem of incomplete conversion observed under an atmosphere of ethylene could be circumvented by diluting the ethylene atmosphere with an inert gas, thereby reducing the number of unproductive metathesis cycles. Although the overall conversion is slightly better if the experiments are run under 12 bars of ethylene and 30 bars of argon (Table 2, entries 13–16), no improvement of the selectivity was observed compared to the previous sets of experiments. Our observations differ somewhat from those recently published by Honda et al. who investigated the double RCM of a tetraene structurally related to **6a**. These authors reported a remarkably strong tendency towards the formation of fused six-membered ring products structurally related to **7a** and **9**, while a dumbbell-type product analogous to **10** could not be accessed selectively. However, only catalysts bearing N-heterocyclic carbene ligands were investigated in this study.[32]

The results discussed above are related to previous reports describing a significant erosion in selectivity of double ring-closing metathesis reactions whenever ruthenium carbenes with an NHC ligand are used as catalysts. This is not limited to ring size-selectivity,[31,45] as in our example, but has also been observed in diastereoselective double RCM reactions.[46–48] However, the level of selectivity towards the formation of bis-dihydrofuran **10** with the first-generation catalyst **A** is quite remarkable.

Regioselective Single RCM: 2,3-Disubstituted Dihydropyrans 7 *vs.* 2-Substituted Dihydrofurans 8

If R in structure **2** is not an allyl group, as required for double RCM, different ring size-selectivities have to be expected if the steric or electronic properties of R are changed. In particular, R might be a bulky protecting group leading to sterically congested intermediates or transition states during the RCM step. For instance, a high degree of ring size-selectivity might be expected if one of the two possible ruthenacyclobutanes **11** (leading to dihydropyrans **7**) or **12** (leading to dihydrofurans **8**) is much more destabilized by steric interactions than the other. Thus, it might be speculated that for **11** steric interactions between the OR group, the vinyl group in 2-position and the ruthenacyclobutane moiety are stronger than for **12**, where the OR group can adopt an orientation away from the ruthenacyclobutane ring, thereby minimizing steric interactions. This should result – if R is



Scheme 5. Proposed influence of different OR groups on ring size-selectivity.

sufficiently bulky – in a faster formation of dihydrofuran **8** compared to the dihydropyran **7**. Alternatively, a coordinating OR group could serve as a catalyst-directing group, which might result in a preferred initiation at the closest C/C double bond "b" in substrates **2**. The resulting carbene complex **13** should then cyclize to dihydropyrans **7** (Scheme 5). Exploiting catalyst-directing effects for regio- or stereoselective synthesis is a well-known principle in homogeneous catalysis, which has been reviewed.[49] For olefin metathesis reactions such effects are less common, although they have been proposed, e.g., for MOM protecting groups.[22] Another variable site of the substrate structure is the terminus of the "a" double bond. Introducing a substituent R' here will disfavor initiation at this particular site and hopefully support a catalyst-directed initiation at "b". An example for the efficient discrimination of one double bond in the initiating step by terminal substitution has been described by Honda et al. for a diene-yne metathesis.[50]

Apart from these substrate-specific parameters, those that have been investigated for the double RCM need to be considered here as well: the nature of the catalyst, the temperature and the pressure might have an influence on the ratio of dihydropyrans **7** to dihydrofurans **8**.

We started this investigation by conducting ring closing metathesis reactions of trienes **6b–h** and **5d** (Table 1) in the presence of 5 mol% of a first- or second-generation ruthenium catalyst. The results are summarized in Table 3. With sterically demanding TBS- or trityl protecting groups, only dihydrofurans **8b** and **c**, respectively, are formed if the less active precatalyst **A** is used (entries 1 and 3). Similar to the pattern observed for the double RCM of tetraene **6a**, a significant erosion of selectivity occurs with the NHC-ligated precatalyst **C**, although it should be

Table 3. Results obtained for the ring size-selective RCM of trienes **6b–h** and **5d** (R′ = H in all cases).

Entry	Triene	R	Catalyst (5 mol %).	Conversion [%][a]	**7**:**8**	Product (yield)[b]
1	**6b**	TBS	**A**	99	< 1:20	**8b** (90 %)
2	**6b**	TBS	**C**	99	1:2	**7b** + **8b**
3	**6c**	CPh_3	**A**	90	< 1:20	**8c** (68 %)
4	**6c**	CPh_3	**C**	99	1:3	**7c** + **8c**
5	**6d**	Bn	**A**	99	1:12	**8d** (88 %)
6	**6d**	Bn	**C**	99	1:1	**7d** + **8d**
7	**6d**	Bn	**C**	< 5[c]	n.d.	–
8	**6d**	Bn	**A**	55[d]	1:7	**8d**
9	**6d**	Bn	**C**	99[d]	1:1	**7d** + **8d**
10	**6e**	Me	**A**	99	1:3	**7e** + **8e**
11	**6e**	Me	**C**	99[e]	1:1	**7e** + **8e**
12	**6f**	CH_2OBn	**A**	99	< 1:20	**8f** (89 %)
13	**6f**	CH_2OBn	**C**	99	1:1	**7f** + **8f**
14	**6g**	CO_2Et	**A**	99	1:10	**8g** (88 %)
15	**6g**	CO_2Et	**C**	99	1:1	**7g** + **8g**
16	**6g**	CO_2Et	**D**	99[f]	1:1	**7g** + **8g**
17	**6g**	CO_2Et	**A**	99 [g]	1:11	**8g**
18	**6g**	CO_2Et	**C**	99 [g]	1:1.3	**7g** + **8g**
19	**6g**	CO_2Et	**A**	99 [h]	1:10	**8g**
20	**6g**	CO_2Et	**A**	99[i]	1:12	**8g**
21	**6g**	CO_2Et	**C**	99[i]	1:1	**7g** + **8g**
22	**6g**	CO_2Et	**D**	99[i]	1:1	**7g** + **8g**
23	**6h**	$COCCl_3$	**A**	99	< 1:20	**8h** (99 %)
24	**6h**	$COCCl_3$	**C**	70	1 : 3	**7h** + **8h**
25	**5d**	H	**A**	90	1:1	**7i** + **8i**
26	**5d**	H	**C**	99[e]	–	–

[a] All reactions were conducted in DCM at ambient temperature (20 °C) with 5 mol % of the appropriate Ru precatalyst. Conversion and product ratios were determined by H NMR-spectroscopy of the crude reaction mixture.
[b] Yields are given in parentheses for isolated, single isomers.
[c] In CH_2Cl_2 at 0 °C.
[d] In toluene at 110 °C
[e] Complex mixture, refer to discussion.
[f] In CH_2Cl_2 at −30 °C.
[g] In CH_2Cl_2 at 80 °C in pressurized vessel.
[h] Addition of CuCl (5 mol %).
[i] Atmosphere of ethene (1 bar).

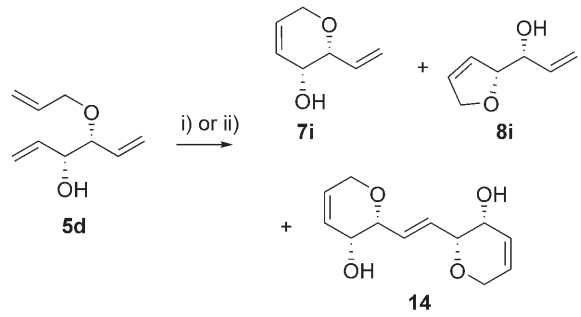
noted that the five-membered ring systems are still preferred (entries 2 and 4). It is in line with the proposal discussed above (Scheme 5) that for a sterically less hindered benzyl ether (**6d**) selectivity drops to 1:12 for precatalyst **A** (entry 5) and to 1:1 for **C** (entry 6). With this substrate we planned to investigate if variation of the temperature exerts a significant influence. It turned out that at 0 °C the second-generation catalyst **C** was virtually inactive, with the rate of conversion being less than 5 % (entry 7). Increasing the temperature to 110 °C (refluxing toluene) did not change the observed pattern significantly: with precatalyst **A** (entry 8), the dihydrofuran **8d** is still the major product, although formed with lower selectivity. However, under these conditions only incomplete conversion is observed, which might be explained by a comparatively rapid decomposition of the catalyst.[51] Incomplete conversion is not a problem if second-generation catalyst **C** is used under identical conditions for the same substrate **6d**. The ratio of **7d** to **8d** is the same as observed at ambient temperature, however, new signals appear in the ^{1}H NMR spectrum which might be assigned to a cyclic enol ether arising from double bond migration.[52,53] Interestingly, no isomerization products were observed for first-generation catalyst **A** under otherwise identical conditions, which is in accord with previously published observations from our group that first-generation catalyst **A** requires additives to be transformed into an active isomerization catalyst.[15] It is most likely that **C** decomposes bimolecularly under the reaction conditions to a ruthenium hydride species,[54] which has previously been postulated as the actual isomerization catalyst.[55,56] The necessity for a certain degree of steric hindrance in the OH protecting group in order to obtain preparatively useful selectivities towards dihydrofurans **8** was strongly underlined when RCM of methyl ether **6e**

was investigated. In this case, selectivity drops even with the first-generation catalyst to 1:3 (entry 10). With second generation catalyst **C**, the selectivity is again 1:1. In this case at least one additional product is formed, which might be a product resulting from self-metathesis of **7e** or **8e**, or a cross-metathesis of **7e** and **8e**. This assumption is supported by the observation that the new product(s) do not contain any terminal alkene groups, which is easily seen from the ^{13}C NMR spectrum (entry 11).

Apart from steric effects, coordinative or electronic effects might have an influence on ring size-selectivity, as outlined above. Alkoxymethyl ethers have previously been proposed as catalyst-directing groups[22] in olefin metathesis and we wanted to examine the influence of such a potentially coordinating protecting group by investigating the outcome of an RCM reaction of BOM-protected **6f**. The result was very similar to those observed for trienes **6b–d** and we can, from these experiments, discover no piece of evidence for a catalyst-directing effect of BOM ethers (entries 12 and 13). Protection of the OH group as a carbonate also results in a metathesis precursor **6g** with a functional group that might also have catalyst-directing effects. Selectivities observed under standard conditions (DCM, 20 °C) were very similar to those previously observed for the other derivatives (entries 14 and 15). Temperature effects were re-examined for this substrate in both directions: as was found for the attempted RCM of **6d**, no conversion was observed with second-generation precatalyst **C** at 0 °C (entry 7). We were therefore surprised to see that, with Grela's catalyst **D**, **6g** is completely converted to its metathesis products *even at −30 °C*. This observation is indicative for the extraordinarily high activity of nitro-substituted catalysts. Somewhat disappointingly, no influence on the ring size-selectivity was observed, compared to the reaction at ambient temperature (entry 16). Conducting the reaction at 80 °C in a pressurized vessel (entries 17 and 18) also results in nearly the same product ratios for both first- and second-generation catalysts. In the following set of experiments (entries 19–22) it was checked whether activation of the metathesis catalyst with copper chloride or addition of an ethylene atmosphere leads to any deviation from the results obtained under standard conditions, but no significant changes could be observed. In an attempt to modify the electronic nature of one C/C double bond of the metathesis substrate, a strongly electron-withdrawing trichloroacetyl group was attached to the hydroxy group and the resulting triene **6h** was subjected to metathesis conditions. The results obtained for first (entry 23) and second (entry 24) generation catalysts resemble those obtained for the sterically demanding protecting groups TBS and trityl (entries 1–4), suggesting that a trichloroacetyl group exerts primarily a steric rather than an electronic influence.

With the results described so far in mind, it was quite unexpected that the unprotected parent diene **5d** did not cyclize with a more or less pronounced selectivity to a dihydrofuran **7i**, but gave **7i** and its isomeric dihydropyran **8i** in a 1:1 ratio. Compounds **7i** and **8i** were also formed with second-generation catalyst **C**, but along with other products. Due to the very complex NMR spectra of the reaction mixtures it was difficult to analyze its composition. In order to make at least a qualitative structural assignment of the new products, the mixture was fractionated by column chromatography. A first fraction contained **7i** and **8i** in a 3:1 ratio. A second fraction contained a single product **14**, which has NMR spectral data similar to those assigned to dihydropyran **8i**, with the striking difference that **14** contains no terminal $=CH_2$ group. In the ^{13}C NMR spectrum six signals, and in the ^{1}H NMR spectrum eight signals are observed, which suggests that **14** is the C_2-symmetrical self-metathesis product of dihydropyran **7i** (Scheme 6). Unfortunately, it was not possible to obtain mass spectrometric evidence that would unambigously prove this structural assignment. A third fraction of the mixture contains additional products which are most likely dimers of **8i** and cross-metathesis products of **7i** and **8i**.

At this point it was possible to access carbon skeletons **I** and **III** (Scheme 1) selectively, while all attempts to obtain a precursor for dihydropyran skeleton **II** selectively by extensive variation of catalysts and reaction conditions failed. Although the RCM experiments with **5d** turned out to be particularly unselective in both directions, as described above, the surprisingly high amount of six-membered ring products was quite striking. This observation can be understood by assuming a catalyst-directing effect of the free OH group, which would cause preferred initiation of the catalyst at double bond "b" (Scheme 5). That ruthenium atoms in metathesis catalysts display a certain oxophilicity, especially to alcohols, is underlined by a number of literature reports, describing,



Scheme 6. *General reagents and conditions*: i) catalyst **A** (5 mol %), CH_2Cl_2, 20 °C (**7i**:**8i** = 1:1); ii) catalyst **C** (5 mol %), CH_2Cl_2, 20 °C (**7i** + **8i** + **14** + unidentified products).

Table 4. Results obtained for the ring size selective RCM of trienes with a terminal substituent at double bond "a" ($R' \neq H$ in all cases).

Entry	Triene	R	R′	Catalyst (5 mol%)	Conversion [%][a]	**7i**:**8i**	Product (yield)[b]
1	**5e**	H	Ph	**A**	25	–[c]	–
2	**5e**	H	Ph	**A**	10	–[c,d]	–
3	**5f**	H	CH_3	**A**	60	>20:1	**7i**
4	**5f**	H	CH_3	**A**	65	>20:1[e]	**7i** (52%)
5	**5f**	H	CH_3	**A**	70	>20:1[d,e]	**7i**
6	**5f**	H	CH_3	**C**	99	–[f]	–
7	**5f**	H	CH_3	**B**	85	>20:1	**7i**
8	**5f**	H	CH_3	**B**	95 [g]	>20:1	**7i** (83%)
9	**5f**	H	CH_3	**B**	75 [h]	>20:1	**7i**
10	**5f**	H	CH_3	**B**	95 [g,h]	>20:1	**7i**
11	**6i**	BOM	CH_3	**A**	10	–	–
12	**6i**	BOM	CH_3	**C**	25	–	–
13	**6i**	BOM	CH_3	**A**	<5[i]	–	–
14	**6i**	BOM	CH_3	**C**	<5[i]	–	–
15	**6i**	BOM	CH_3	**A**	<5[j]	–	–
16	**6i**	BOM	CH_3	**C**	<5[j]	–	–
17	**6j**	$COCCl_3$	CH_3	**A**	<5	–	–
18	**6j**	$COCCl_3$	CH_3	**C**	<5	–	–

[a] All reactions were conducted in DCM at ambient temperature (20°C) with 5 mol% of the appropriate Ru precatalyst unless otherwise stated. Conversion and product ratios were determined by H NMR-spectroscopy of the crude reaction mixture.
[b] Yields are given in parentheses for isolated, single isomers.
[c] Unidentified product formed along with unreacted starting material.
[d] 10 mol% of catalyst used.
[e] In CH_2Cl_2 at 40°C.
[f] complex mixture of products obtained, refer to discussion.
[g] In CH_2Cl_2 at 40°C.
[h] 2.5 mol% of catalyst used.
[i] In toluene at 110°C.
[j] In CH_2Cl_2 at 110°C in a pressurized vessel.

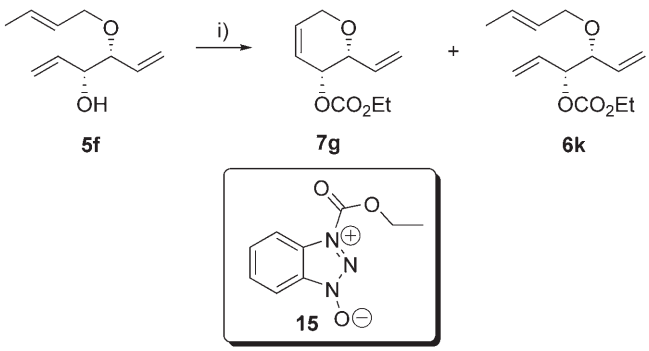
e.g., the formation of chelates if hydroxyalkyl side chains are attached to ligands,[57,58] alkoxy-substitued ruthenium carbenes,[59] or the significant rate enhancement of **A** upon addition of phenols.[60] The interaction of hydroxy groups with metathesis catalysts can, however, also be a source of trouble, as it is known that alcohols induce a degradation of Grubbs' catalysts to ruthenium hydride species,[61–63] that may catalyze isomerization[64] or degradation[65] of the substrate.[52,53] However, in our experiments we could not detect any products resulting from an undesired non-metathesis transformation of the unprotected alcohol **5d**.

Three reasons might exist for the still comparatively large amount of dihydrofuran **8i** in the reaction mixtures: a) the proposed catalyst directing effect is not very strong, resulting in a certain amount of initiation at double bond "c"; b) initiation occurs to a large extent at the least hindered double bond "a" and the resulting carbene complex cyclizes preferably under kinetic control to five-membered ring products; c) initiation occurs with high selectivity at the double bond "b", but a rapid intermolecular transfer to "c" or "a" takes place prior to ring closure. Although the latter scenario has been discussed by Quinn et al. for the RCM of related acrylates,[24] we believed that it would not play a major role in our case, as ring-closing metathesis of allyl ethers is normally much faster than the analogous process for acrylates. Thus, if there is a significant catalyst directing effect, this should result in a high selectivity towards six-membered ring products, if initiation at double bond "a" is reduced.

As outlined in Scheme 5, this can be achieved by attaching a substituent R' to the terminus of double bond "a". To check whether this would result in improved selectivities towards dihydropyrans **8**, we investigated the selectivity of RCM reactions of trienes **5e**, **5f**, **6i** and **6j**. The results are summarized in Table 4. At the beginning, ring-closing metathesis of cinnamyl ether **5e** with first generation catalyst **A** was investigated. Double bonds bearing a terminal phenyl substituent have recently been employed in a number of RCM reactions. Although these proceed with the liberation of non-volatile styrene, good yields have often been reported.[66] In our case, however, only poor conversions of 25% or 10%, respectively, were

observed (entries 1 and 2). Furthermore, it turned out to be quite difficult to analyze the ^{1}H-NMR spectra of the crude reaction mixture, because additional signals appear that cannot be assigned to **5e**, **7i** or **8i**. It might be possible that a cross-metathesis product of **7i** or **8i** with styrene is formed in small amounts. As the reactivity of the double bond "a" is obviously too strongly reduced with a terminal phenyl group, we investigated the RCM of crotyl ether **5f**. Under standard conditions, the desired dihydropyran **7i** was the only product. However, conversion was only 60% with first generation catalyst **A** (entry 3) and could be improved only slightly by heating the mixture to 40°C or by using 10 mol% of catalyst (entries 4 and 5). Nevertheless, it was possible to obtain pure **7i** by column chromatography in an isolated yield of 52% from these reactions. Using the more active catalyst **C** resulted in full conversion of the starting material (entry 6), but at the expense of selectivity: a complex mixture of products was obtained which contained, among other products, the homodimeric dihydropyran **14** (similar to table 3, entry 26). We were able to obtain significantly better conversions and isolated yields while maintaining the high level of selectivity towards dihydropyran **8i** by using the precatalyst **B**, where the catalytically active species is stabilized by a hemilabile benzylidene ligand. Under standard conditions, the conversion is 85% for **B**, compared to 60% for **A** (entry 7). This value increases to more than 95% at 40°C (entry 8). It is even possible to reduce the amount of catalyst to 2.5 mol%: at ambient temperature, a conversion of 75% and at 40°C a conversion of more than 95% is observed (entries 9 and 10). It is in line with the proposed catalyst-directing effect of the free OH group in **5f** that its protection results in a dramatic decrease of conversion. Under various conditions (entries 11 to 18), neither BOM-protected **6i** nor trichloroacetate **6j** could be converted to RCM products in significant amounts. This observation suggests that the OH group does not only direct the catalyst to a certain site of the molecule, but that it also leads to an overall activation of the molecule to RCM.

Dihydropyran **7i** is quite volatile which makes it necessary to take special precautions during chromatography and work-up. We thought it might be more practical to functionalize the free OH group *in situ* and trap the dihydropyran as a less volatile derivative. To this end, **5f** was treated with precatalyst **A** as described above, and – after conversion had ceased – the reaction mixture containing unreacted **5f** and dihydropyran **7i** was treated with oxybenzotriazole carbamate (**15**).[67,68] The products **7g** and **6k** were isolated by column chromatography without taking any precautions against loss of material by evaporation (Scheme 7). The sequence might also be practical from the synthetic point of view, as the carbonate



Scheme 7. *Reagents and conditions*: i) catalyst **A** (5 mol%), CH_2Cl_2, 20°C; add **15** (2.0 equivs. relative to **5f**), pyridine, triethylamine and DMAP; separate by column chromatography (43% of **7g** and 56% of **6k**).

group in **7g** can serve as a leaving group in Pd-catalyzed transformations. Such a sequence is a convenient entry into the stereoselective synthesis of 2,5-*cis*-disubstituted dihydropyrans.[69,70]

Conclusions

Starting from a conveniently available chiral building block, hexadienediol **1**, various tri- and tetraenes have been prepared and subjected to ring-closing metathesis reactions using different catalysts and conditions. We have successfully realized our goal to make both dihydrofurans and dihydropyrans accessible from the same precursors *via* a ring size-selective RCM reaction. In summary, it can be stated that the effect of temperature and pressure on the product ratios is negligible. Significant differences were observed for first- and second-generation catalysts, with the first generation catalysts being generally more selective. Another significant influence on the selectivity of the reaction is exerted by the OH protecting group. A combination of first-generation catalyst and a bulky protecting group yields five-membered rings with virtually perfect selectivity, whereas the free alcohol – in combination with first generation catalysts – cyclizes selectively to dihydropyrans. We propose a catalyst-directing effect of the allylic hydroxy group as a rationale for the selectivity patterns observed in this study. Further investigations of such effects in olefin metathesis reactions and their exploitation for control of selectivity issues are currently in progress in our laboratory.

Experimental Section

General Remarks

Experiments were conducted in dry reaction vessels under an atmosphere of dry argon. Solvents were purified by stan-

dard procedures. ^{1}H NMR spectra were recorded on a Bruker Avance 300, Bruker Avance DRX 400, Bruker Avance DRX 500, or Varian Inova 600 in $CDCl_3$ or benzene-d_6. Chemical shifts (δ) are reported in ppm relative to TMS with $CHCl_3$ ($\delta_H = 7.24$ ppm, $\delta_C = 77.0$ ppm) or C_6D_5H ($\delta_H = 7.18$ ppm, $\delta_C = 128.0$ ppm) as internal standard. Coupling constants (J) are given in Hertz. In ^{13}C NMR spectra the number of coupled protons was analyzed by APT or DEPT experiments and is denoted by a number in parentheses following the δ_C value. IR spectra were recorded as films on NaCl or KBr plates. The peak intensities are defined as strong (s), medium (m) or weak (w). Mass spectra were obtained at 70 eV. The following compounds have previously been described in the literature: **5a**,[24] **5b**,[22] **5c**.[23]

Synthesis of Dienediol 1 from D-Mannitol

(*2R,3S,4S,5R*)-2,3,4,5-Tetraacetoxy-1,6-dibromohexane (3):[20] D-Mannitol (54.7 g, 0.300 mol) is suspended in dry dioxane (600 mL) under an argon atmosphere. Acetyl bromide (88.9 g, 0.723 mol) is added slowly, and stirred for 4 d at room temperature. A clear, yellowish solution is formed. After 4 d, the solution is heated to 40 °C and stirred at that temperature for another 4 h. The solvent and other volatiles are removed under vacuum. The viscous residue is dissolved in anhydrous pyridine (300 mL), and acetic anhydride (245.0 g, 2.400 mol) is added slowly. The solution is stirred overnight at room temperature. Pyridine and other volatiles are removed under vacuum. The greenish residue is crystallized from a small amount of ethanol (approx. 50 mL) to afford **3** as a white, crystalline solid; yield: 71.2 g (50 %); mp 120–122 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 5.35$ (2 H, d, $J = 8.1$ Hz, 3-H, 4-H), 5.04 (2 H, m, 2-H, 5-H), 3.48 (2 H, dd, $J = 11.6$, 3.8 Hz, 1-$H_{2,a}$), 3.30 (2 H, dd, $J = 11.6$, 6.0 Hz, 1-$H_{2,b}$), 1.98–2.10 (12 H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 168.7$, 168.6 (0, C=O), 68.2, 68.0 (1, O-CH), 29.7 (2, Br-CH_2), 19.8, 19.7 (3, CH_3); $[\alpha]_D^{20}$: +29.6 (c 0.95, CH_2Cl_2).

(*3R,4R*)-3,4-Diacetoxy-1,5-hexadiene (4): Compound **3** (50.2 g, 0.105 mol) is dissolved in glacial acetic acid (525 mL). Sodium acetate (19.0 g, 0.232 mol) and zinc dust (27.5 g, 0.421 mol) are added. The mixture is heated to 110 °C, and stirred until the evolution of gas has ceased and the solution becomes clear (approx. 1 h). After cooling, the zinc dust is filtered off and the acetic acid is removed under vacuum. The viscous, colorless residue is dissolved in water and extracted three times with diethyl ether (150 mL). The combined organic layers are washed with saturated aqueous $NaHCO_3$ solution (***caution:*** vigorous evolution of gas!), dried over magnesium sulfate, and the solvent is removed under vacuum. The colorless crude product is distilled under vacuum (bp 59–61 °C, 0.8 mbar) to afford **4** as a colorless liquid; yield: 17.7 g (89.3 mmol, 85 %). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 5.72$ (2 H, ddd, $J = 17.2$, 10.7, 6.0 Hz, −HC=), 5.37 (2 H, d, $J = 5.1$ Hz, −OCH−), 5.30 (2 H, d, $J = 17.2$ Hz, =$CH_{2,trans}$), 5.24 (2 H, d, $J = 10.7$ Hz, =$CH_{2,cis}$), 2.05 (6 H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 169.7$ (0, C=O), 132.0 (1, −HC=), 119.1 (2, =CH_2), 74.3 (1, OCH), 20.9 (3, CH_3).

(*3R,4R*)-3,4-Dihydroxy-1,5-hexadiene [(*R,R*)-1]:[21] Compound **4** (13.0 g, 65.0 mmol) is dissolved in methanol (260 mL), and an aqueous solution of potassium carbonate (2 M, 4 mL) is added. The progress is monitored by TLC (eluent: *n*-hexane:ethyl acetate, 1:1). After full conversion (approx. 30 min), aqueous HCl (1 M, 8 mL) is added in 1 mL portions. The mixture is dried over magnesium sulfate, and the solvent is carefully removed under reduced pressure (100 mbar, 40 °C) until the solution becomes turbid. Diethyl ether is added and the solution is dried over magnesium sulfate again. The solvent is removed under vacuum and the yellowish crude product is distilled under vacuum (bp 43 °C, 0.4 mbar) to afford (*R,R*)-**1** as a colorless oil; yield: 6.40 g (86 %). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 5.83$ (2 H, ddd, $J = 17.2$, 10.6, 5.6 Hz, −HC=), 5.33 (2 H, d, $J = 17.2$ Hz, =$CH_{2,trans}$), 5.22 (2 H, d, $J = 10.6$ Hz, =$CH_{2,cis}$), 3.97 (2 H, m, OCH), 2.80 [2 H, s(br), OH]; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 136.5$ (1, −HC=), 117.3 (2, =CH_2), 75.7 (1, OCH); $[\alpha]_D^{20}$: +41.0 (c 0.98, CH_2Cl_2).

Selective Mono-Etherification of Diol 1 *via* Formation of a Stannylene Acetal

(*3R,4R*)-3-(Allyloxy)-4-hydroxyhexa-1,5-diene (5d): A Dean–Stark tube, which is filled with MS 4 Å, is charged with **1** (615 mg, 5.4 mmol) in benzene (65 mL). Di-*n*-butyltin oxide (1.48 g, 5.9 mmol) and Bu_4NI (497 mg, 1.35 mmol) are added and heated to reflux until formation of water stops (approx. 1.5 h). The mixture is cooled below its boiling point, the Dean–Stark tube is removed, and allyl bromide (1.0 mL, 11.6 mmol) is added. The mixture is heated to reflux for 16 h. If the conversion is incomplete after this time, additional allyl bromide (1.0 mL, 11.6 mmol) is added and the mixture is again heated to reflux for 6 h. After cooling to ambient temperature, diethyl ether (40 mL) is added and the mixture is washed carefully with aqueous sodium thiosulfate solution (10 %, 50 mL). The aqueous phase is extracted three times with diethyl ether (50 mL each). The combined organic phases are washed with water (50 mL), dried over magnesium sulfate, and all volatiles are removed under vacuum. After column chromatography (silica, pentane:diethyl ether 15:1→7:1), **5d** is obtained as a colourless liquid; yield: 709 mg (85 %). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 5.88$ (1 H, dddd, $J = 16.4$, 10.3, 5.1, 0.9 Hz, −HC=), 5.79 (1 H, ddd, $J = 17.1$, 10.5, 5.8 Hz, −HC=), 5.64 (1 H, ddd, $J = 17.3$, 10.4, 7.8 Hz, −HC=), 5.36–5.14 (6 H, =CH_2), 4.09 (1 H, dddd, $J = 12.7$, 5.1, 1.5, 1.5 Hz, $OCH_{2,a}$), 4.01 (1 H, dd, $J = 6.5$, 6.5 Hz, OCH), 3.85 (1 H, ddd, $J = 12.7$, 6.2, 1.3, 1.3 Hz, $OCH_{2,b}$), 3.58 (1 H, dd, $J = 6.6$, 6.5 Hz, OCH), 2.81 [1 H, s(br), OH]; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 136.0$, 134.6, 134.4 (1, −HC=), 119.9, 117.3, 117.0 (2, =CH_2), 83.8, 74.6 (1, OCH), 69.4 (2, OCH_2); ; $[\alpha]_D^{20}$: −20.4 (c 1.04, CH_2Cl_2); IR (film): ν = 3462 [m (br)], 3081 (m), 2983 (m), 2864 (s), 1867 (w), 1646 (m), 1423 (s), 1343 (m), 1255 (m), 1121 (s), 1075 (vs), 992 (vs), 926 (vs) cm^{-1}; MS (ESI): $m/z = 137$ (M^+−OH, 100 %); 105 (20 %), 81 (75 %); HR-MS (FAB): m/z = 177.0900, calcd. for $C_9H_{14}O_2Na$ (M^+ + Na): 177.0891.

(*3R,4R*)-3-(Cinnamyloxy)-4-hydroxyhexa-1,5-diene (5e): Following the procedure given for **5d**, **5e** was obtained from **1** (1.90 g, 16.2 mmol) and cinnamyl bromide (3.82 g, 19.4 mmol); yield: 1.60 g (43 %). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.43$–7.24 (5 H, C_{Ar}-H), 6.63 (1 H, d, J = 16.1 Hz, Ph-H_{trans}C=), 6.30 (1 H, ddd, $J = 15.9$, 6.5, 5.7 Hz, PhCH=*CH*-), 5.87 (1 H, ddd, $J = 17.2$, 10.5, 5.7 Hz, −HC=), 5.75 (1 H, ddd, $J = 18.3$, 10.5, 7.7 Hz, −HC=), 5.43–5.31 (3 H, =CH_2), 5.24 (1 H, ddd, $J = 10.5$, 1.7, 1.4 Hz, =$CH_{2,cis}$), 4.31

(1H, ddd, $J=12.6$, 5.7, 1.6 Hz, $OCH_{2,a}$), 4.10 (1H, m, OCH), 4.07 (1H, ddd, $J=12.6$, 6.6, 1.3 Hz, $OCH_{2,b}$), 3.70 (1H, dd, $J=7.5$, 7.5 Hz, HO-*CH*), 2.89 [1H, s(br), OH]; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=136.6$ (0), 136.1, 134.7, 132.6, 128.5, 127.7, 126.5, 125.7 (1, C_{Ar}-H and −HC=), 119.9, 116.9 (2, $=CH_2$), 83.8, 74.6 (1, OCH), 69.2 (2, OCH_2); $[\alpha]_D^{20}$: −17.2 (*c* 1.40, CH_2Cl_2); IR (film): $\nu=3439$ [s (br)], 3026 (m), 2863 (m), 1876 (w), 1702 (m), 1495 (s), 1422 (s), 1049 (s), 991 (s) cm^{-1}; MS (EI): $m/z=117$ (82, $PhCHCHCH_2^+$), 57 (100); HR-MS (FAB): $m/z=253.1213$, calcd. for $C_{15}H_{18}O_2Na$ (M^++Na): 253.1204.

(*3R,4R*)-3-(Crotyloxy)-4-hydroxyhexa-1,5-dien (5f): Following the procedure given for **5d**, **5f** was obtained from **1** (2.28 g, 20 mmol) and crotyl bromide (4.9 mL, 40 mmol) as a 4:1 mixture of *E*/*Z*-isomers; yield: 2.92 g (88%). NMR data are given for the major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=5.79$ (1H, ddd, $J=17.2$, 10.6, 1.8 Hz, −HC=), 5.72–5.51 (3H, −HC=), 5.36–5.16 (4H, $=CH_2$), 4.15–3.91 (2H, OCH, $OCH_{2,a}$), 3.77 (1H, ddt, $J=11.5$, 6.5, 0.9 Hz, $OCH_{2,b}$), 3.56 (1H, dd, $J=7.7$, 7.7 Hz, OCH), 2.80 [1H, s (br), OH], 1.70 (3H, dd, $J=6.4$, 1.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=136.0$, 134.7, 130.0, 127.1 (1, −HC=), 119.8, 117.0 (2, $=CH_2$), 83.6, 74.6 (1, OCH), 69.3 (2, OCH_2), 17.8 (3, CH_3); $[\alpha]_D^{20}$: −24.1 (*c* 1.47, CH_2Cl_2); IR (film): $\nu=$ 3465 [m (br)], 3022 (m), 2860 (m), 1728 (w), 1644 (w), 1423 (m), 1257 (w), 1047 (s), 992 (s), 927 (s) cm^{-1}; MS (ESI): $m/z=151.3$ (M^+−OH, 100%); 138.3 (80%); 123.4 (50%); anal. calcd. for $C_{10}H_{16}O_2$: C 71.4%, H 9.6%; found: C 71.0%, H 9.6%.

Alkylation of Sodium Alkoxides (Williamson Ether Synthesis)

(*3R,4R*)-3,4-Bis(allyloxy)hexa-1,5-diene (6a): To a solution of **1** (770 mg, 6.7 mmol) in anhydrous THF (49 mL) is added NaH (60% dispersion in paraffin, 750 mg, 18.9 mmol), and the resulting suspension is heated to reflux for 1 h. The mixture is cooled below its boiling point, and allyl bromide (1.80 mL, 20.2 mmol) is added. The mixture is again heated to reflux until TLC (silica, *n*-hexane:MTBE 10:1) indicates full conversion. After cooling to ambient temperature the mixture is poured onto saturated NH_4Cl solution, extracted three times with MTBE (20 mL each), washed with brine (15 mL) and dried over magnesium sulfate. After evaporation of the solvents under vacuum, the residue is purified by flash chromatography (silica, *n*-hexane:MTBE 15:1) to give **6a** as a colourless liquid; yield: 1.13 g (5.84 mmol, 87%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=5.88$ (2H, ddd, $J=16.3$, 10.7, 5.6 Hz, −HC=), 5.74 (2H, m, −HC=), 5.27–5.21 (6H, $=CH_2$), 5.13 (2H, dd, $J=10.4$, 1.4 Hz, $=CH_{2,cis}$), 4.08 (2H, ddt, $J=13.0$, 3.7, 1.4 Hz, OCH_{2a}), 3.91 (2H, ddm, $J=13.0$, 6.0 Hz, $OCH_{2,b}$), 3.81 (2H, m, OCH); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=135.2$, 135.0 (1, −HC=), 118.2, 116.6 (2, $=CH_2$), 82.2 (1, OCH), 69.9 (2, OCH_2); $[\alpha]_D^{20}$: −3.2 (*c* 1.49, CH_2Cl_2); IR (film): $\nu=3080$ (w), 2925 (m), 2859 (m), 1732 (w), 1645 (m), 1424 (m), 1262 (w), 1124 (s), 1080 (vs), 992 (s), 925 (vs) cm^{-1}; MS (FAB): no M^+ peak could be detected.

(*3R,4R*)-3-(Benzyloxy)-4-allyloxyhexa-1,5-diene (6d): Following the procedure given for **6a**, **6d** was obtained from **5c** (472 mg, 2.3 mmol) and allyl bromide (0.40 mL, 4.6 mmol); Yield: 545 mg (97%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.38$–7.25 (5H, Ph), 5.95–5.75 (3H, −CH=), 5.32–5.24 (5H, $=CH_2$), 5.16 (1H, d, $J=10.4$ Hz, $=CH_2$), 4.67 (1H, d, $J=12.1$ Hz, $OCH_{2,a}$-Ph), 4.48 (1H, d, $J=12.1$ Hz, $OCH_{2,b}$-Ph), 4.12 (1H, dd, $J=13.2$, 2.8 Hz, $OCH_{2,a}$−CH=), 3.95 (1H, dd, $J=13.2$, 5.8 Hz, OCH_{2b}−CH=), 3.87 (2H, dm, $J=3.9$ Hz, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=138.6$ (0, *ipso*-C), 135.2, 135.1, 135.0, 128.2, 127.6, 127.4 (1, C_{Ar}-H and −HC=), 118.5, 118.2, 116.6 (2, $=CH_2$), 82.3, 82.2 (1, OCH), 70.7, 69.9 (2, OCH_2); $[\alpha]_D^{20}$: −7.42 (*c* 0.51, CH_2Cl_2); IR (film): $\nu=3346$ (w), 3078 (m), 3029 (m), 2982 (m), 2863 (s), 1645 (w), 1454 (m), 1423 (m), 1345 (m), 1069 (vs), 992 (vs), 927 (vs) cm^{-1}; MS (FAB): $m/z=245$ (M^++H, 10%); 243 (5%); 197 (15%); 91 (100%); HR-MS (FAB): $m/z=245.1512$, calcd. for $C_{16}H_{21}O_2$ (M^++H): 245.1542.

(*3R,4R*)-3-(Methoxy)-4-allyloxyhexa-1,5-diene (6e): Following the procedure given for **6a**, **6e** was obtained from **5d** (308 mg, 2.0 mmol) and methyl iodide (0.13 mL, 2.0 mmol); yield: 202 mg (60%); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=5.86$ (1H, ddd, $J=17.1$, 11.2, 6.1 Hz, −CH=), 5.76–5.66 (2H, −CH=), 5.26–5.19 (5H, $=CH_2$), 5.12 (1H, ddd, $J=10.3$, 1.3, 1.3 Hz, $=CH_{2,cis}$), 4.07 (1H, ddd, $J=12.9$, 5.2, 1.4 Hz, $OCH_{2,a}$), 3.88 (1H, ddd, $J=13.0$, 6.1, 1.2 Hz, $OCH_{2,b}$), 3.77 (1H, m, OCH), 3.60 (1H, m, OCH), 3.29 (1H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ =135.1, 134.9, 134.8 (1, −CH=), 118.6, 118.5, 116.8 (2, $=CH_2$), 84.8, 82.0 (1, OCH), 69.6 (2, OCH_2), 56.9 (3, OCH_3); $[\alpha]_D^{20.5}$: −9.50 (*c* 1.37, CH_2Cl_2); IR (film): $\nu=3080$ (m), 2983 (s), 2933 (s), 2871 (s), 2359 (w), 1864 (w), 1731 (s), 1645 (m), 1423 (s), 1331 (w), 1086 (vs), 927 (vs) cm^{-1}; MS (FAB or ESI): no M^+ peak could be detected.

Pd-Catalyzed *O*-Allylation

(*3R,4R*)-3-(*tert*-Butyldimethylsilyloxy)-4-allyloxyhexa-1,5-diene (6b): In an oven-dried Schlenk tube, **5a** (228 mg, 1.0 mmol) is dissolved in anhydrous THF (5 mL). In a second Schlenk tube, allyl ethyl carbonate (260 mg, 2.0 mmol) and $Pd(PPh_3)_4$ (28.8 mg, 2.5 mol%) are dissolved in THF and transferred to the substrate solution *via* a teflon cannula. The reaction mixture is heated to reflux and the conversion is monitored by TLC (silica, cyclohexane:MTBE, 5:1). After complete conversion, the reaction mixture is cooled and filtered through a short pad of silica, followed by washing with MTBE. After evaporation of all volatiles the residue is purified by flash chromatography, affording **6b** as a colorless liquid; yield: 200 mg (74%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=5.92$–5.80 (2H, −HC=), 5.67 (1H, ddd, $J=$ 17.3, 10.7, 7.1 Hz, −HC=), 5.27–5.17 (4H, $=CH_2$), 5.14–5.09 (2H, $=CH_2$), 4.17 (1H, dd, $J=5.7$, 5.7 Hz, OCH), 4.05 (1H, dd, $J=12.9$, 5.1 Hz, $OCH_{2,a}$), 3.89 (1H, dd, $J=13.0$, 5.9 Hz, $OCH_{2,b}$), 3.66 (1H, t, $J=6.5$ Hz, OCH), 0.88 [9H, s, Cq-(CH_3)$_3$], 0.06 [3, s, Si-$(CH_3)_{2a}$], 0.03 [3, s, Si-$(CH_3)_{2b}$]; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=137.5$, 137.3, 135.1 (1, −HC=), 118.1, 116.5, 115.4 (2, $=CH_2$), 83.7, 75.2 (1, OCH), 69.8 (2, OCH_2), 25.8 [3, Cq-(CH_3)$_3$], 18.2 (0, Si-C_q), −4.7 [3, Si-$(CH_3)_{2,a}$], −4.8 [3, Si-$(CH_3)_{2,b}$]; $[\alpha]_D^{20}$: +37.3 (*c* 1.01, $CHCl_3$); IR (film): $\nu=3080$ (w), 2929 (s), 2857 (s), 1645 (w), 1472 (m), 1423 (w), 1361 (w), 1253 (s), 1086 (s), 1034 (s), 991 (m), 925 (s), 837 (s), 776 (s), 673 (w) cm^{-1}; MS (CI): $m/z=269$ (M^++H, 100%); 211 (100%); 171 (60%); 137 (20%); 97 (15%); anal. calcd. for $C_{15}H_{28}O_2Si$: C 67.1%, H 10.5%; found: C 66.4%, H 10.1%.

(*3R,4R*)-3-(Triphenylmethoxy)-4-allyloxyhexa-1,5-diene (6c): Following the procedure given for **6b**, **6c** was obtained from **5b** (1.07 g, 3.0 mmol); yield: 980 mg (82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.53–7.48 (6H, Ar-H), 7.29–7.19 (9H, Ar-H), 5.86–5.72 (3H, −HC=), 5.22–4.99 (6H, =CH_2), 4.21 (1H, m, OCH), 3.68 (1H, ddd, J = 12.9, 1.5, 1.3 Hz, $OCH_{2,a}$), 3.50 (1H, ddd, J = 12.9, 1.4, 1.3 Hz, $OCH_{2,b}$), 2.84 (1H, m, OCH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 144.8 (0, *ipso*-C), 135.7, 134.8, 129.1, 127.7, 127.0, 127.0 (1, C_{Ar}, −CH=), 118.0, 116.2, 116.2 (2, =CH_2), 87.6 (0, OC_q), 80.5, 75.3 (1, OCH), 69.5 (2, OCH_2); $[\alpha]_D^{20}$: +54.8 (*c* 0.63, CH_2Cl_2); IR (film): ν = 3059 (m), 2923 (m), 2360 (w), 1960 (w), 1734 (w), 1644 (m), 1597 (m), 1491 (s), 1448 (s), 1043 (s), 923 (s) cm^{-1}; anal. calcd. for $C_{28}H_{28}O_2$: C 84.8%, H 7.1%; found: C 84.2%, H 7.0%.

Protection as BOM Ether, Carbonate or Trichloroacetate

(*3R,4R*)-3-(Benzyloxymethoxy)-4-allyloxyhexa-1,5-diene (6f): At 0°C, **5d** (771 mg, 5.0 mmol) is dissolved in dichloromethane, then ethyldiisopropylamine (3.30 mL, 20.0 mmol) and benzyloxymethyl chloride (BOM chloride, 2.50 mL, 18.0 mmol) are added. The mixture is allowed to warm to ambient temperature and stirred for 16 h. It is diluted with MTBE (60 mL), washed twice with saturated aqeous Na_2CO_3 solution, dried over magnesium sulfate and all volatiles are removed under vacuum. After flash chromatography (silica, cyclohexane:MTBE, 40:1→20:1), **6f** is obtained as a colorless liquid; yield: 945 mg (69%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.35–7.26 (5H, Ar-H), 5.90 (1H, ddd, J = 16.5, 10.6, 5.3 Hz, −HC=), 5.85–5.76 (2H, −HC=), 5.32–5.24 (5H, =CH_2), 5.14 (1H, dd, J = 10.4, 1.3 Hz, =$CH_{2,cis}$), 4.79 (2H, s, O*CH*$_2$O), 4.73 (1H, d, J = 11.6 Hz, $OCH_{2,a}$-Ph), 4.54 (1H, d, J = 11.6, $OCH_{2,b}$-Ph), 4.20 (1H, dd, J = 6.3, 6.3 Hz, OCH), 4.11 (1H, dd, J = 13.0, 5.0 Hz, $OCH_{2,a}$CH=), 3.91 (1H, dd, J = 13.0, 6.0 Hz, $OCH_{2,b}$CH=), 3.82 (1H, dd, J = 6.4, 6.4 Hz, OCH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 137.9 (0, *ipso*-C), 135.3, 134.9, 134.7, 128.4, 128.1, 127.6 (1, C_{Ar}-H, −HC=), 118.6, 118.6, 116.7 (2, =CH_2), 92.2 (2, O*CH*$_2$O), 82.3, 79.1 (1, OCH), 69.8, 69.4 (2, OCH_2); $[\alpha]_D^{20}$: −61.0 (*c* 0.87, CH_2Cl_2); IR (film): ν = 3079 (m), 2886 (s), 2248 (w), 1868 (w), 1645 (m), 1455 (s), 1424 (s), 1382 (m), 1038 (vs), 928 (vs) cm^{-1}; MS (FAB): *m/z* = 276 (M^++H, 6%); 167 (50%); 137 (35%); 91 (100%); HR-MS (FAB): *m/z* = 275.1618, calcd. for $C_{17}H_{23}O_3$ (M^++H): 275.1647; anal. calcd. for $C_{17}H_{22}O_3$: C 74.4%, H 8.1%; found: C 74.1%, H 8.1%.

(*3R,4R*)-3-(Benzyloxymethoxy)-4-crotyloxyhexa-1,5-diene (6i): Following the procedure given for **6f**, **6i** was obtained from **5f** (841 mg, 5.0 mmol); yield: 1.03 g (71%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.34–7.26 (5H, Ar-H), 5.84–5.76 (2H, −HC=), 5.70–5.53 (2H, −HC=), 5.31–5.24 (4H, =CH_2), 4.78 (2H, s, OCH_2Ph), 4.72 (1H, d, J = 11.7 Hz, $OCH_{2,a}$), 4.53 (1H, d, J = 11.7 Hz, $OCH_{2,b}$), 4.18 (1H, dd, J = 6.8, 6.8 Hz, OCH), 4.02 (1H, dd, J = 11.8, 5.8 Hz, $OCH_{2,a2}$), 3.86–3.78 (2H, OCH, $OCH_{2,b2}$), 1.67 (3H, dd, J = 6.4, 1.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 137.9 (0, *ipso*-C), 135.6, 134.8, 129.0, 128.3, 128.0, 127.7, 127.6 (1, C_{Ar}, −HC=), 118.5, 118.3 (2, =CH_2), 92.2 (2, OCH_2O), 82.0, 79.1 (1, OCH), 69.7, 69.4 (2, OCH_2), 17.7 (3, CH_3); $[\alpha]_D^{20}$: −45.1 (*c* 0.95, CH_2Cl_2). IR (film): ν = 3066 (w), 3029 (m), 2885 (m), 1644 (w), 1454 (m), 1097 (s), 1040 (vs), 928 (s) cm^{-1}; MS (FAB): *m/z* = 290 (M^++H, 7%); 181 (30%); 197 (15%); 91 (100%); 56 (25%); HR-MS (FAB): *m/z* = 289.1815, calcd. for $C_{18}H_{25}O_3$ (M^++H): 289.1804; anal. calcd. for $C_{18}H_{24}O_3$: C 75.0%, H 8.4%; found: C 74.6%, H 8.5%.

(*3R,4R*)-3-(Ethoxycarbonyloxy)-4-allyloxyhexa-1,5-diene (6g): Compound **5d** (2.29 g, 14.8 mmol) is dissolved in dry diethyl ether (15 mL) and cooled to 0°C. Pyridine (2.42 mL, 29.6 mmol), followed by ethyl chloroformate (1.42 mL, 14.8 mmol) are added slowly. The cooling bath is removed, and after 1 h, the mixture is heated to reflux until TLC (silica, pentane:diethyl ether 9:1) indicates complete conversion. Aqueous HCl (1M, 10 mL) is added. The resulting aqueous layer is extracted three times with diethyl ether (25 mL each). The combined organic layers are washed with brine (25 mL) and dried over magnesium sulfate. After removal of all volatiles under vacuum and column chromatography (silica, pentane:diethyl ether 10:1), **6g** is obtained as a pale yellow oil; yield: 2.63 g (79%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.89–5.77 (2H, −CH=), 5.68 (1H, m, −CH=), 5.36–5.21 (5H, =CH_2), 5.15–5.11 (2H, =CH_2 and EtO-CO_2CH), 4.18 (2H, q, J = 7.1, OCO_2CH_2), 4.05 (1H, dd, J = 13.0, 5.0 Hz, $OCH_{2,a}$), 3.88 (1H, dd, J = 13.0, 5.9 Hz, $OCH_{2,b}$), 3.86 (1H, dd, J = 6.7, 6.7 Hz, OCH), 1.28 (3H, t, J = 7.1, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 154.5 (0, OCO_2); 134.6, 133.9, 132.4 (1, −HC=), 119.7, 118.8, 116.8 (2, =CH_2), 80.8, 79.2 (1, OCH), 69.7, 64.0 (2, OCH_2), 14.2 (3, CH_3); $[\alpha]_D^{20}$: +16.6 (*c* 1.20, CH_2Cl_2); IR (film): ν = 3082 (w), 2985 (m), 2858 (m), 1748 (vs), 1647 (m), 1424 (m), 1372 (s), 1256 (vs), 1082 (s), 995 (s), 930 (s), 876 (m) cm^{-1}; MS (FAB): *m/z* = 227 (M^++H, 50%); 137 (100%); 97 (90%); 42 (65%); HR-MS (FAB): *m/z* = 227.1299, calcd. for $C_{12}H_{19}O_4$ (M^++H): 227.1284

(*3R,4R*)-3-(Trichloroacetoxy)-4-allyloxyhexa-1,5-diene (6h): Compound **5d** (771 mg, 5.0 mmol) is dissolved in dry dichloromethane (5 mL) and cooled to 0°C. Triethylamine (1.4 mL, 10.0 mmol), DMAP (24 mg, 0.2 mmol), and trichloroacetyl chloride (0.61 mL, 6.0 mmol) are added. The mixture is stirred at 0°C for 30 min, then it is warmed to 20°C and stirred for another 30 min. It is diluted with MTBE (5 mL) and hydrolyzed with saturated aqueous Na_2CO_3 solution (10 mL). The aqueous layer is extracted with MTBE (15 mL), and the combined organic layers are washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL), and dried over magnesium sulfate. After evaporation of all volatiles and column chromatography (silica, pentane:diethyl ether, 40:1→20:1), **6h** is obtained as a yellowish liquid; yield: 250 mg (1.15 mmol, 23%), along with recovered starting material **5d** (364 mg, 2.35 mmol, 47%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.88–5.80 (2H, −HC=), 5.67 (1H, ddd, J = 16.4, 11.1, 7.4 Hz, −HC=), 5.44 (1H, d, J = 17.3 Hz, =$CH_{2,trans}$), 5.40–5.31 (4H, =CH_2, CO_2CH), 5.24 (1H, dd, J = 17.3, 1.6 Hz, =$CH_{2,trans}$), 5.15 (1H, dd, J = 10.4, 1.4 Hz, =$CH_{2,cis}$), 4.09 (1H, ddt, J = 12.9, 5.1, 1.5 Hz, $OCH_{2,a}$), 3.94 (1H, dd, J = 7.1, 7.1 Hz, OCH), 3.89 (1H, ddt, J = 12.9, 6.0, 1.3 Hz, $OCH_{2,b}$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 160.9 (0, CO_2), 134.3, 133.2, 130.8 (1, −HC=), 120.5, 120.1, 117.1 (2, =CH_2), 90.1 (0, CCl_3), 80.6, 80.5 (1, OCH), 69.9 (2, OCH_2); $[\alpha]_D^{20}$: +7.8 (*c* 1.02, CH_2Cl_2); IR (film): ν = 3083 (w), 2986 (w), 2864 (m), 1770 (vs), 1647 (m), 1424 (m), 1243 (vs), 1084 (s), 987 (s), 934 (s), 826 (s), 680 (s) cm^{-1}; MS (FAB): *m/z* = 299 (M^+, 8%); 98 (40%); 80 (35%); 42

(30%); anal. calcd. for $C_{11}H_{13}O_3Cl_3$: C 44.1%, H 4.4%; found: C 44.4%, H 4.5%.

(*3R,4R*)-3-Trichloroacetoxy-4-crotyloxyhexa-1,5-diene (6j): Following the procedure given for **6h**, **6j** was obtained from **5f** (841 mg, 5.0 mmol); yield: 0.42 g (27%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 5.85$ (1H, ddd, $J = 17.2$, 10.7, 6.4 Hz, $-HC=$), 5.74–5.65 (2H, $-HC=$), 5.54 (1H, m, $-HC=$), 5.45 (1H, d, $J = 17.2$ Hz, $=CH_{2,trans}$), 5.40–5.32 (4H, $=CH_2$, CO_2CH), 4.03 (dd, $J = 12.0$, 3.7 Hz, $OCH_{2,a}$), 3.95 (1H, dd, $J = 7.0$, 7.0 Hz, OCH), 3.85 (1H, dd, $J = 11.9$, 6.6 Hz, $OCH_{2,b}$), 1.69 (3H, d, $J = 6.4$ Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 160.9$ (0, CO_2), 133.4, 130.9, 129.6, 127.1 (1, $-HC=$), 120.1, 120.0 (2, $=CH_2$), 90.1 (0, CCl_3), 80.7, 80.2 (1, OCH), 69.8 (2, OCH_2), 17.7 (3, CH_3); $[\alpha]_D^{20}$: +17.7 (*c* 0.96, CH_2Cl_2); IR (film): $\nu = 3085$ (w), 3021 (w), 2919 (m), 2860 (m), 1769 (vs), 1647 (w), 1426 (m), 1242 (vs), 1095 (m), 983 (m), 935 (m), 839 (s), 826 (s) cm^{-1}; MS (FAB): $m/z = 313$ ($M^+ + H$, <5%); 281 (15%); 207 (20%); 147 (50%); 74 (100%); anal. calcd. for $C_{12}H_{15}O_3Cl_3$: C 46.0%, H 4.8%; found: C 46.0%, H 4.9%.

Ring Size-Selective Double RCM

Selectivity studies: Double RCM reactions were conducted with **6a** (19.4 mg, 0.1 mmol) and the appropriate precatalyst **A**–**E** (5 mol%) and solvent (2.0 mL, refer to Table 2 for specific conditions) in standardized sealable tubes in four parallel runs. If required, the reaction mixtures were heated in a stainless steel heating block. For reactions at higher pressures, the open reaction vessels were kept in a Parr autoclave, the appropriate pressure was applied and the whole autoclave was heated with an external heating mantle. The solvent was subsequently evaporated, and the residue was analyzed by ^{1}H NMR spectroscopy. Product ratios were determined by comparison of the integrals for the AB system of the OC*HH* protons.

(4a*R*,8a*R*)-2,4a,6,8a-Tetrahydropyrano[3,2-*b*]pyran (9): The title compound was obtained in pure form by careful chromatographic removal of bis-dihydrofuran **10** in sufficient amounts to allow complete NMR spectroscopic characterization. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 6.08$ (2H, dd, $J = 10.2$, 3.4 Hz, 5-H), 5.95 (2H, m, 4-H), 4.27 (2H, ddd, $J = 16.8$, 3.8, 1.6 Hz, 6-$H_{2,a}$), 4.14 (2H, dd, $J = 16.8$, 1.1 Hz, 6-$H_{2,b}$), 3.73 (2H, m, 2-H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 131.9$ (1, C-5), 123.7 (1, C-4), 67.8 (1, C-2), 65.4 (2, C-6); $[\alpha]_D^{20}$: +202.7 (*c* 0.44, $CHCl_3$); IR (film): $n = 3040$ (w), 2945 (m), 2854 (m), 2813 (s), 2703 (w), 1682 (w), 1440 (m), 1382 (s), 1342 (s), 1302 (s), 1177 (s), 1084 (s), 856 (s) cm^{-1}; MS: no M^+ peak detectable with EI, FAB or ESI methods.

(*R*)-2,5-Dihydro-2-[(*R*)-2,5-dihydrofuran-2-yl]furan (10); preparative scale: Compound **6a** (388 mg, 2.0 mmol) is dissolved in anhydrous dichloromethane (40 mL), and catalyst **A** (5 mol%, 82 mg) is added. After stirring for 16 h at 20°C, the solvent is removed under reduced pressure and the residue is purified by flash chromatography (silica, cyclohexane:MTBE, 2:1) to give **10**; yield: 189 mg (49%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 6.00$ (2H, dd, $J = 6.3$, 1.5 Hz, 3-H), 5.74 (2H, m, 4-H), 4.82 (2H, m, 2-H), 4.69–4.60 (4H, 5-H_2); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 128.6$, 126.1 (1, -HC=), 88.0 (1, C-2), 75.8 (2, C-5); $[\alpha]_D^{20} = +217.0$ (*c* 0.44, $CHCl_3$); IR (film): $\nu = 3081$ (w), 2850 (s), 2359 (w), 1726 (m), 1456 (w), 1382 (w), 1348 (w), 1262 (w), 1074 (s), 1019 (m), 812 (w), 712 (m) cm^{-1}; MS: no M^+ peak detectable with EI, FAB or ESI methods.

Ring Size -Selective Single RCM

Selectivity studies: These were performed using the same methods and instrumentation as described above for the double ring closing metathesis reactions. Results are summarized in Table 3 for allyl ethers **5d** and **6b**–**h** and in Table 4 for crotyl ethers **5f** and **6i,j** and cinnamyl ether **5e**.

Preparative scale: In those cases where the selectivity study on 0.1 mmol scale revealed a preparatively useful selectivity towards five- or six-membered ring products ($\geq$ 10:1), the reaction was repeated on a $\geq$1 mmol scale following the procedure given above for the synthesis of **10**.

RCM Products of 5d–f

RCM of hydroxy derivative 5d: RCM of **5d** catalyzed by **A** according to the procedure given above for selectivity studies resulted in the formation of dihydropyran **7i** and dihydrofuran **8i** as an inseparable 1:1 mixture. Selected NMR spectroscopic data were obtained from the mixture.

(*R*)-2-[(*R*)-1-Hydroxyallyl]-2,5-dihydrofuran (**8i**): ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.00$ (1H, dm, $J = 6.2$ Hz, $-HC=CH-$), 5.86 (1H, ddd, $J = 17.2$, 10.5, 5.9 Hz, $-HC=CH_2$), 5.75 (1H, d, $J = 6.2$ Hz, $-HC=CH-$), 4.70 (1H, m, OCH), 4.72–4.61 (2H, OCH_2), 4.01 (1H, m, $OCHCH=$); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 135.0$, 130.1, 126.6 (1, $-HC=$), 117.0 (2, $=CH_2$), 89.2 (1, OCH), 75.5 (2, OCH_2), 75.3 (1, OCH).

RCM of **5d** catalyzed by **C** according to the procedure given above for selectivity studies resulted in the formation of a more complex mixture, containing – apart from **7i** and **8i** – a third product which could be isolated in very small amounts by column chromatography and was identified as self-metathesis product *E*-bis-[(2*R*,3*R*)-3,6-dihydro-3-hydroxy-2*H*-pyran-2-yl]-ethene (**14**): ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 6.04$ (2H, dm, $J = 10.1$ Hz, $-HC=CH-$); 5.95 [2H, s (br), $-HC=$), 5.93 (2H, dm, $J = 10.1$ Hz, $-CH=CH-$), 4.28 (2H, dm, $J = 17.0$ Hz, OCH_2), 4.18 (2H, dm, $J = 17.0$ Hz, OCH_2), 4.10 [2H, s (br), OCH], 3.86 (2H, m, OCH), 2.33 [2H, s(br), OH]; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 130.1$, 129.3, 126.5 (1, $-HC=$), 77.4 (1, OCH), 66.0 (2, OCH_2), 64.1 (1, OCH).

RCM of cinnamyl ether 5e: RCM of **5e** catalyzed by **A** according to the procedure given above for selectivity studies resulted in a conversion of less than 10% at ambient temperature. At 40°C or in the presence of catalyst **C** conversion was approximately 40%. In all cases very complex product mixtures resulted which were difficult to analyze.

RCM of crotyl ether 5f; ***(2R,3R)*-3,6-dihydro-2-vinyl-*2H*-pyran-3-ol (7i):** Compound **5f** (1.79 g, 10.6 mmol) was dissolved in dichloromethane (200 mL). Catalyst **A** (437 mg, 5 mol%) was added and the reaction mixture was stirred overnight. The solvent was evaporated under vacuum, and the dark brown residue purified by column chromatography, followed by Kugelrohr distillation (oven temperature 50°C at 0.23 mbar), to give **7i** as a colorless oil; yield: 697 mg (52%). Conversion (as judged from the NMR spectrum of the crude mixture) is 65%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.05$ (1H, dddd, $J = 10.2$, 5.4, 2.4, 2.2 Hz, $-HC=CH-$), 5.97 (ddd, 1H, $J = 17.4$, 10.8, 5.4 Hz, $-CH=CH_2$), 5.94 (1H, ddd, $J = 10.2$, 3.5, 1.5 Hz, $-CH=CH<C->$), 5.39 (1H, ddd, $J =$

17.4, 1.6, 1.6 Hz, $=CH_{2,trans}$), 5.30 (1H, ddd, $J=10.8$, 1.5, 1.5 Hz, $=CH_{2,cis}$), 4.28 (1H, ddd, $J=17.1$, 3.4, 1.8 Hz, OCH_2), 4.19 (1H, ddd, $J=17.1$, 3.8, 1.6 Hz, OCH_2), 4.02 (1H, m, OCH), 3.84 [1H, m, OCH(OH)], 1.84 [1H, s (br), OH]; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=135.0$, 130.2, 126.6 (1, −CH=), 117.2 (2, $=CH_2$), 78.4 (1, OCH), 66.0 (2, OCH_2), 64.5 [1, OCH(OH)]; $[\alpha]_D^{20}$: −200.1 (*c* 0.93, CH_2Cl_2); IR (film): $\nu=$ 3435 [m (br)], 2926 (s), 2853 (m), 2245 (w), 1648 (w), 1446 (m), 1091 (s), 929 (m), 734 (s) cm^{-1}; MS (FAB): $m/z=127.1$ ($[M+H]^+$, 20%); 109.3 ($[M-OH]^+$, 50%); anal. calcd. for $C_7H_{10}O_2$: C 66.7%, H 8.0%; found: C 66.2%, H 8.1%.

Improved conversion (95%, as judged by NMR) is observed when **5f** (168 mg, 1.0 mmol) is treated with catalyst **B** (30 mg, 5 mol%) at 40°C. Following the procedure described above for the RCM of **5f** with **A**, **7i** was obtained as the only product; yield: 105 mg (83%).

RCM of crotyl ether 5f with *in situ* derivatization; Ethyl (*2R*,*3R*)-3,6-dihydro-2-vinyl-*2H*-pyran-3-yl carbonate (7g): Following the procedure given above for the synthesis of **7i**, **5f** (336 mg, 2.0 mmol) was treated with catalyst **A** (82 mg, 5 mol%). After 4 h, the mixture was filtered through a short pad of silica using diethyl ether as eluent. All volatiles were evaporated. The crude product was dissolved in pyridine (8 mL), and triethylamine (0.83 mL, 6.9 mmol), oxybenzotriazole carbamate (**15**) (829 mg, 4.0 mmol) and DMAP (24 mg, 10 mol%) were added. The mixture was stirred at 20°C for 14 h, then water (10 mL) was added, and the resulting aqueous layer was extracted three times with ethyl acetate (10 mL each). The combined organic layers were dried over magnesium sulfate, all volatiles were removed under vacuum and the residue was chromatographed on silica (pentane:diethyl ether, 2:1) to give **7g** (yield: 170 mg, 43%) and **6k** (yield: 270 mg, 56%) as colorless liquids.

Analytical data for **7g**: ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=6.09$ (1H, dm, $J=10.2$ Hz, −*H*C=CH−), 6.00 (1H, dm, $J=$ 10.2 Hz, −HC=C*H*−), 5.90 (1H, ddd, $J=17.3$, 10.7, 5.5 Hz, −*H*C=CH_2), 5.40 (1H, d, $J=17.3$ Hz, $=CH_{2,trans}$), 5.25 (1H, d, $J=10.7$ Hz, $=CH_{2,cis}$), 4.94 [1H, m, C*H*O(OCO_2Et)], 4.34 (1H, d, $J=17.1$ Hz, OCH_2), 4.22–4.13 (4H, OCH_2, OCH_2CH_3, OCH), 1.26 (3H, t, $J=7.1$ Hz, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=155.0$ (0, *C*O_2Et), 133.6, 132.8, 122.0 (1, −HC=), 117.6 (2, $=CH_2$), 76.4, 69.3 (1, OCH), 65.4, 64.0 (2, OCH_2), 14.2 (3, -CH_3); $[\alpha]_D^{20}$: −183.6 (*c* 0.86, CH_2Cl_2); IR (film): $\nu=2984$ (w), 2937 (w), 2824 (w), 1741 (s), 1372 (m), 1257 (s), 1095 (s), 1011 (s), 819 (m) cm^{-1}; MS (FAB): no M^+ peak observed; anal. calcd. for $C_{10}H_{14}O_4$: C 60.6%, H 7.1%; found: C 60.7%, H 7.5%.

Analytical data for **6k**: ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=$ 5.81 (1H, ddd, $J=17.2$, 10.6, 6.5 Hz, −HC=), 5.70–5.62 (2H, −HC=), 5.51 (1H, m, −HC=), 5.35–5.23 (4H, $=CH_2$), 5.12 [1H, dd, $J=6.4$ Hz, OC*H*(OCO_2Et)], 4.17 (2H, q, $J=$ 7.1 Hz, OCH_2CH_3), 4.00 (1H, dd, $J=11.9$, 5.7 Hz, OCH_2), 3.87–3.79 (2H, OCH_2, OCH), 1.67 (3H, d, $J=6.4$ Hz, =CH-CH_3), 1.28 (3H, t, $J=7.1$ Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=154.5$ (0, *C*O_2Et), 134.1, 132.5, 129.3, 127.4 (1, −HC=), 119.4, 118.8 (2, $=CH_2$), 80.5, 79.3 (1, OCH), 69.6, 64.0 (2, OCH_2), 17.7, 14.2 (3, -CH_3); $[\alpha]_D^{20}$: +21.3 (*c* 0.55, CH_2Cl_2); IR (film): $\nu=2934$ (w), 2859 (w), 1748 (s), 1371 (m), 1256 (s), 1092 (m), 995 (m), 790 (w) cm^{-1}; anal. calcd. for $C_{13}H_{20}O_4$: C 65.0%, H 8.4%; found: C 64.7%, H 8.2%.

RCM Products of 6b–h

(*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)allyl]-2,5-dihydrofuran (8b): Obtained from **6b** (274 mg, 1.0 mmol) using catalyst **A** (41 mg, 5 mol%) as a colorless liquid; yield: 222 mg (90%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=5.92$ (1H, dd, $J=$ 6.2, 1.4 Hz, −HC=), 5.79 (1H, ddd, $J=17.2$, 10.5, 5.6 Hz, −*H*C=CH_2), 5.77 (1H, d, $J=5.4$ Hz, −HC=), 5.24 (1H, d, $J=17.2$ Hz, $=CH_{2,trans}$), 5.11 (1H, d, $J=10.5$ Hz, $=CH_{2,cis}$), 4.75 (1H, m, OCH), 4.59–4.57 (2H, OCH_2), 4.15 (1H, dd, $J=5.2$, 5.2 Hz, OC*H*CH=), 0.88 [9H, s, C(CH_3)$_3$], 0.05 [3H, -Si(CH_3)$_{2,a}$], 0.02 [3H, -Si(CH_3)$_{2,b}$]; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=137.5$, 127.9, 126.7 (1, −HC=), 115.7 (2, $=CH_2$), 89.5, 75.6 (1, OCH), 75.7 (2, OCH_2), 25.8 [3, −C(CH_3)$_3$], 18.2 (0, SiC_q), −4.7, −4.9 [3, -Si(CH_3)$_2$]; $[\alpha]_D^{20}$: +79.1 (*c* 0.66, CH_2Cl_2); IR (film): $\nu=2956$ (s), 2930 (s), 2857 (s), 1763 (m), 1472 (m), 1254 (s), 1138 (m), 1081 (vs), 1034 (m) cm^{-1}; HR-MS (FAB): $m/z=263.1441$, calcd. for $C_{13}H_{24}O_2NaSi$ (M^++Na): 263.1443.

(*R*)-2-[(*R*)-1-(Triphenylmethoxy)allyl]-2,5-dihydrofuran (8c): Obtained from **6c** (397 mg, 1.0 mmol) using catalyst **A** (41 mg, 5 mol%) as a colorless liquid; yield: 251 mg (68%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.52$–7.48 (6H, Ar), 7.29–7.19 (9H, Ar), 5.92–5.86 (2H, OCH), 5.57 (1H, ddd, $J=$ 17.5, 10.6, 7.0 Hz, −*H*C=CH_2), 4.86 (1H, dd, $J=17.5$, 0.6 Hz, $=CH_{2,trans}$), 4.80 (1H, d, $J=10.6$ Hz, $=CH_{2,cis}$), 4.52–4.42 (2H, OCH_2), 4.34 (1H, m, OCH), 4.11 (1H, dd, $J=5.9$, 5.9 Hz, OC*H*CH=); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=144.8$ (0, *ipso*-C), 135.8, 129.1, 128.6, 127.8, 127.6, 127.5, 127.0, 126.9 (1, C_{Ar}, −HC=), 115.9 (2, $=CH_2$), 87.6 (1, OCH), 87.3 (0, OC_q), 76.8 (1, OCH), 75.8 (2, OCH_2); $[\alpha]_D^{20}$: +100.1 (*c* 0.75, CH_2Cl_2); IR (film): $\nu=3058$ (m), 2917 (m), 2849 (m), 1620 (w), 1490 (m), 1448 (s), 1078 (s), 1049 (s), 917 (m) cm^{-1}; HR-MS (FAB): m/z=391.1684, calcd. for $C_{26}H_{24}O_2Na$ (M^++Na): 391.1674.

(*R*)-2-[(*R*)-1-(Benzyloxy)allyl]-2,5-dihydrofuran (8d): Obtained from **6d** (242 mg, 1.0 mmol) using catalyst **A** (41 mg, 5 mol%) as a colorless liquid; yield: 190 mg (88%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=7.38$–7.26 (5H), 5.97 (1H, d, $J=6.2$ Hz), 5.84–5.75 (2H), 5.36–5.30 (2H), 4.93 (1H, m), 4.67 (1H, d, $J=12.2$ Hz), 4.65–4.61 (2H), 4.47 (1H, d, $J=$ 12.2 Hz), 3.85 (1H, dd, $J=6.7$, 6.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=138.5$ (0, *ipso*-C), 135.0, 128.2, 128.1, 127.5, 127.3, 126.5 (1, C_{Ar}, −*C*H=), 119.2 (2, $=CH_2$), 88.0, 82.3 (1, O*C*H), 75.6, 70.4 (2, OCH_2); IR (film): $\nu=3064$ (w), 3030 (w), 2863 (m), 1774 (m), 1454 (m), 1071 (s), 932 (m), 808 (w) cm^{-1}; $[\alpha]_D^{20}$: +29.2 (*c* 1.12, CH_2Cl_2); MS (FAB): $m/z=$ 217.0 ($[M+H]^+$, 8%); 215.0 ($[M-H]^+$, 5%); 91.6 (100%); HR-MS (FAB): m/z=217.1235, calcd. for $C_{14}H_{17}O_2$ (M^++H^+): 217.1229.

RCM of methoxy derivative 6e: RCM of **6e** catalyzed by **A** according to the procedure given above for selectivity studies resulted in the formation of dihydropyran **7e** and dihydrofuran **8e** as an inseparable 1 : 3 mixture. NMR-spectroscopic data were obtained from the mixture.

(2*R*, 3*R*)-3-Methoxy-2-vinyl-3,6-dihydro-2*H*-pyran (**7e**): ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=6.07$–5.98 (2H, −*H*C=C*H*−), 5.67 [1H, m, −*H*C=CH_2 (not resolved due to signal overlap)], 5.38 (1H, dm, $J=17.3$ Hz, $=CH_{2,trans}$), 5.26 (1H, dm, $J=10.3$ Hz, $=CH_{2,cis}$), 4.31 (1H, d, $J=16.3$ Hz, OCH_2), 4.15 (1H, d, $J=16.3$ Hz, OCH_2), 4.04 [1H, m, OC*H*(CH=CH_2)], 3.62 [1H, m, OC*H*(OCH_3)], 3.38 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=135.0$, 130.8, 123.6 (1, −

CH=), 116.8 (2, $=CH_2$), 78.0, 72.5 (1, OCH), 65.4 (2, OCH_2), 56.5 (3, OCH_3).

(*R*)-2-[(*R*)-1-Methoxyallyl)-2,5-dihydrofuran (**8e**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.95 (1H, dm, J = 6.2 Hz, −*H*C=CH−), 5.74 (1H, dm, J = 6.2 Hz, −HC=C*H*−), 5.68 [1H, m, −*HC*=CH_2 (not resolved due to signal overlap)], 5.29 (1H, d, J = 10.3 Hz, $=CH_{2,cis}$), 5.28 (1H, d, J = 17.1 Hz, $=CH_{2,trans}$), 4.81 (1H, m, OCH), 4.67–4.58 (2H, OCH_2), 3.57 [1H, dd, J = 6.9, 6.9 Hz, OC*H*(OCH_3)], 3.31 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 134.7, 128.2, 126.4 (1, −CH=), 119.5 (2, $=CH_2$), 87.9, 85.3 (1, OCH), 75.6 (2, OCH_2), 56.7 (3, OCH_3).

(*R*)-2-[(*R*)-1-(Benzyloxymethoxy)allyl]-2,5-dihydrofuran (8f): Obtained from **6f** (274 mg, 1.0 mmol) using catalyst **A** (41 mg, 5 mol%) as a colorless liquid; yield: 220 mg (89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.25 (5H, Ar-H), 5.98 (1H, dd, J = 6.2, 1.7 Hz, −HC=), 5.78 (1H, m, −HC=), 5.75 (1H, ddd, J = 17.7, 10.4, 9.5 Hz, −*HC*=CH_2), 5.32 (1H, d, J = 17.7 Hz, $=CH_{2,trans}$), 5.28 (1H, d, J = 11.2 Hz,$=CH_{2,cis}$), 4.88 (1H, m, OCH), 4.81 (1H, d, J = 6.9 Hz, OCH_2Ph), 4.78 (1H, d, J = 6.9 Hz, OCH_2Ph), 4.72 (1H, d, J = 11.7 Hz, OCH_2OCH_2Ph), 4.68–4.59 (2H, OCH_2), 4.54 (1H, d, J = 11.7 Hz, OCH_2OCH_2Ph), 4.14 (1H, dd, J = 6.6, 6.6 Hz, O-*CH*-CH=); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.9 (0, *ipso*-C), 134.4, 128.4, 128.3, 127.9, 127.6, 126.4 (1, C_{Ar}, −HC=), 119.2 (2, $=CH_2$), 92.1 (2, OCH_2O), 88.0, 79.2 (1, O*C*H), 75.6, 69.3 (2, OCH_2); $[\alpha]_D^{20}$: −19.5 (*c* 0.58, CH_2Cl_2); IR (film): ν = 2976 (w), 2883 (m), 1733 (w), 1455 (w), 1384 (w), 1101 (m), 1042 (s), 927 (m) cm^{-1}.

(*R*)-2-[(*R*)-1-(Ethoxycarbonyloxy)allyl]-2,5-dihydrofuran (8g): Obtained from **6g** (234 mg, 1.0 mmol) using catalyst **A** (41 mg, 5 mol%) as a colorless liquid; yield: 216 mg (88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.01 (1H, dd, J = 6.3, 1.9 Hz, −*H*C=CH−), 5.82 (1H, ddd, J = 17.3, 10.6, 6.3 Hz, −*H*C=CH_2), 5.73 (1H, dm, J = 6.3 Hz, −HC=C*H*−), 5.37 (1H, d, J = 17.3 Hz, $=CH_{2,trans}$), 5.28 (1H, d, J = 10.6 Hz, $=CH_{2,cis}$), 5.06 [1H, dd, J = 6.6, 5.6 Hz, OC*H*(CH=CH_2)], 4.89 (1H, m, OC*H*), 4.68–4.57 (2H, OCH_2), 4.16 (2H, q, J = 7.1 Hz, OCH_2CH_3); 1.27 (3H, t, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.5 [0, C(=O)], 132.4, 129.4, 125.3 (1, −HC=), 119.3 (2, $=CH_2$), 86.8, 79.7 (1, O*C*HCH=), 75.7, 64.0 (2, OCH_2), 14.2 (3, -CH_3); $[\alpha]_D^{20}$: +56.9 (*c* 2.12, CH_2Cl_2); IR (film): ν = 3087 (w), 2984 (m), 2857 (m), 1746 (vs), 1467 (w), 1373 (m), 1259 (s), 1083 (m), 1009 (m), 928 (w), 882 (w) cm^{-1}; MS (FAB): m/z = 199 (M^++H, 45%), 197 (40%), 154 (30%), 109 (100%); HR-MS (FAB): m/z = 197.0797, calcd. for $C_{10}H_{13}O_4$ (M^+−H): 197.0841.

(*R*)-2-[(*R*)-1-(Trichloroacetoxy)allyl]-2,5-dihydrofuran (8h): Obtained from **6h** (300 mg, 1.0 mmol) using catalyst **A** (41 mg, 5 mol%) as a colorless liquid; yield: 270 mg (99%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.06 (1H, dm, J = 6.2 Hz, −*H*C=CH−), 5.91 (1H, ddd, J = 17.2, 10.6, 6.6 Hz, −*H*C=CH_2), 5.73 (1H, dm, J = 6.2 Hz, −HC=C*H*−), 5.47 (1H, d, J = 17.3 Hz, $=CH_{2,trans}$), 5.38 (1H, d, J = 10.6 Hz, $=CH_{2,cis}$), 5.34 [1H, dd, J = 5.5, 5.5 Hz, OC*H*(CH=CH_2)], 4.97 (1H, m, OC*H*), 4.69 (1H, ddm, J = 13.0, 5.9 Hz, OCH_2), 4.63 (1H, dm, J = 13.0 Hz, OCH-); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 161.1 (0, CO_2CCl_3), 131.1, 130.2, 124.6 (1, −HC=), 120.2 (2, $=CH_2$), 86.6, 80.8 (1, O*C*H), 76.0 (2, OCH_2), 63.6 (0, CCl_3); $[\alpha]_D^{20}$: +83.9 (*c* 0.94, CH_2Cl_2); IR (film): ν = 2859 (m), 2360 (m), 2341 (m), 1767 (vs), 1243 (vs), 1085 (s), 982 (m), 944 (m), 827 (s), 680 (s) cm^{-1}; MS: no M^+ peak detectable with EI, FAB or ESI methods.

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