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Diastereoselectivity in a Ring Closing Metathesis Reaction with a Remote Stereogenic Centre Leading to Quaternary Dihydropyrans

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Abstract—Starting from α-allyloxy esters, divinyl carbinols with diastereotopic vinyl groups become accessible. Diastereoselectivity for ring closing metathesis reactions of these trienes was investigated. Formation of a spirocyclic derivative proceeds with significant diastereoselectivity, and a mechanistic proposal for the diastereoselective formation of spirocyclic derivatives is presented. © 2000 Elsevier Science Ltd. All rights reserved.

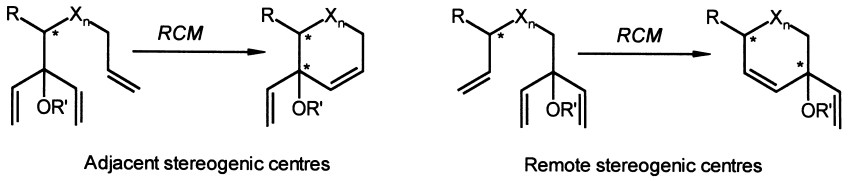
Introduction

The discovery of ruthenium carbene complexes as efficient catalysts for ring closing metathesis by Grubbs et al.[1–3] has led to a manifold of different applications of this synthetic method.[4–6] Thus, over the past few years ring closing metathesis turned out to be an efficient tool for the preparation of medium-sized and large carba- and heterocycles. In the field of heterocyclic chemistry the majority of contributions deal with the synthesis of oxa- and azacycles, and many efforts were made to develop synthetic methodologies for suitably functionalized precursors. If metathesis precursors are chiral (racemic or non-racemic) and contain diastereotopic vinyl or allyl groups, ring closing metathesis may in principle become a diastereoselective process. The first example for this approach was described by Blechert et al. for a highly diastereoselective ring closing metathesis leading to five membered azacycles.[7] More recently decaline derivatives[8] and oxepines annellated to a carbohydrate scaffold[9] were synthesized via diastereoselective ring closing metathesis. A diastereoselective synthesis of dihydropyrans with two adjacent stereogenic centres starting from α-hydroxy esters was investigated by us.[10]

The objective of this study is to find out if significant diastereoselectivity in the formation of dihydropyrans requires the presence of an adjacent stereogenic centre, or if remote stereocentres will also lead to a significant diastereoselection. Scheme 1 schematically illustrates the different approaches.

Results and Discussion

The metathesis precursors required for this study were prepared starting from allylic alcohol **1**.[11] Alkylation of **1** with ethyl-2-bromoacetate in the presence of NaH as a base has to be carried out at 0°C, otherwise a Wittig rearrangement leading to a α-hydroxy ester **3** occurs. Treatment of **3** with excess vinylmagnesium chloride yields the divinylcarbinol **4**, along with 10% of the ketone **5**, resulting from a 1,4-addition. The yield of **4** and **5** is quantitative, however, isolation of **4a** by column chromatography leads to a decrease of the yield to 52%, probably due to acid mediated decomposition of the divinylcarbinol. Variation of the steric demand of the hydroxy substituent in **4a** was achieved by introduction of different protecting groups. This derivatization



Scheme 1.

Keywords: diastereoselectivity; dihydropyrans; metathesis reaction.

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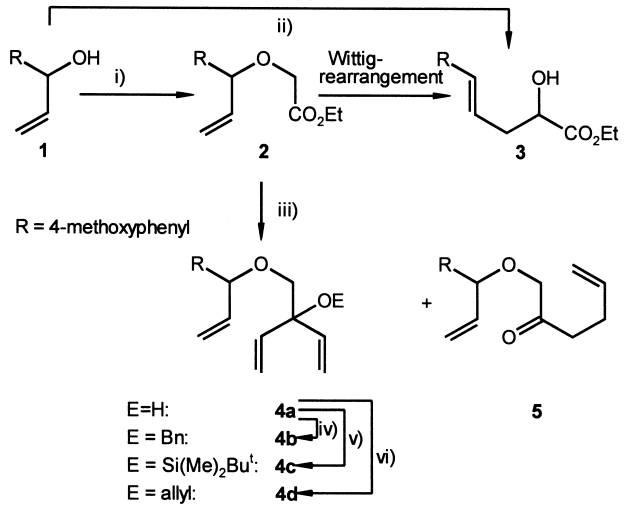
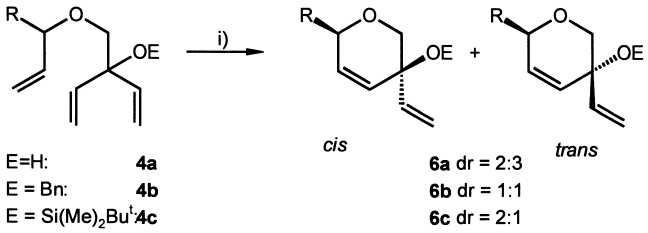


Scheme 2. (i) NaH (1.3 equiv.), THF, 65°C, then 0°C, add ethyl-2-bromopropionate (1.3 equiv.), 20 min (76%); (ii) NaH (1.3 equiv.), THF, 65°C, then 0°C, add ethyl-2-bromopropionate (1.3 equiv.), 30 min., add NaH (1.3 equiv.), 2 h; (iii) $H_2C{=}CHMgCl$, Et_2O, −60°C, (52% of **4a**); (iv) NaH (3 equiv.), THF, 65°C, 1 h, then benzyl bromide (3 equiv.), 65°C, 2 h (88%); (v) NaH (3 equiv.), THF, 65°C, 1 h, then TBDMSCl (3 equiv.), 65°C, 10 min. (86%); (vi) NaH (3 equiv.), THF, 65°C, 1 h, then allyl bromide (3 equiv.), 65°C, 2 h (78%).

results, whereas for the benzyl- and TBDMS derivative the *cis*-isomer is very slightly preferred (Scheme 3).

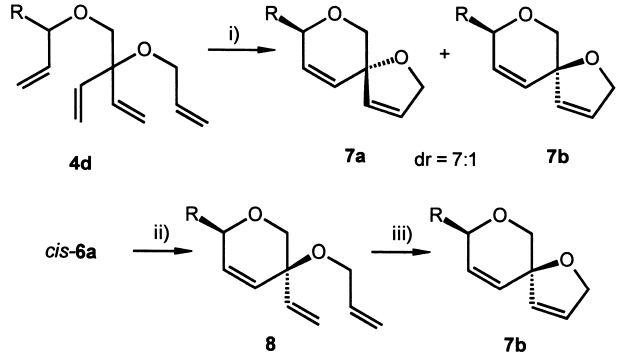
Comparison of these results to those obtained by ourselves for dihydropyrans and by Lautens for substituted cyclohexenes[8] suggests, that a substituent in the neighbouring position to the newly formed stereogenic centre is required to obtain a significant diastereoselectivity, whereas a 1,4-distance of the two stereocentres does not seem to cause a noticeable diastereoselection. If, however, tetraene **4d** reacts with the ruthenium catalyst, the spirocycles **7** are formed in a diastereomeric ratio of 7:1 (Scheme 4).[12] This is surprising, since the allyl substituent in **4d** is definitely sterically less demanding than a benzyl- or a TBDMS group, and hence should not lead to any diastereoselection. **7b** may also be prepared from *cis*-**6a** by allylation to give ether **8** and subsequent ring closing metathesis, whereas this option does not exist for the *trans*-diastereomer, which rapidly decomposes upon attempted allylation. The relative configuration of **7a** and **7b** was elucidated by NOESY experiments conducted for both diastereomers. In both cases a NOE interaction between H2 and $H6_{ax}$ indicates that the sterically demanding aryl substituent adopts an equatorial position. In the minor diastereomer **7b** an additional NOE between $H6_{ax}$ and the olefinic hydrogen of the dihydrofuran



Scheme 3. (i) $Cl_2(PCy_3)_2Ru{=}CHPh$, 7 mol% (84% yield) for **6a**, 7 mol% (81% yield) for **6b**, 10 mol% (80% yield) for **6c**.

requires rather harsh conditions (excess of base, high temperatures, prolonged reaction times), nevertheless no isomerization of the allylic double bond into conjugation with the aromatic substituent is observed (Scheme 2).

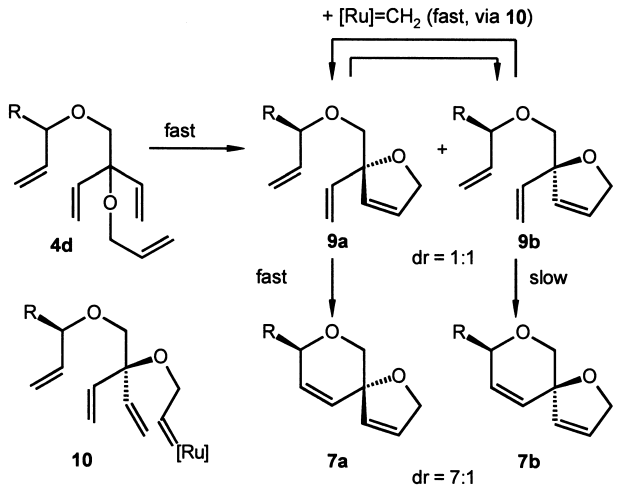
If trienes **4a**–**c** are subjected to ring closing metathesis, only very poor diastereoselectivities are observed. In the case of **4a** an easily separable 2:3 mixture of *cis*- and *trans*-**6a**



Scheme 4. (i) $Cl_2(PCy_3)_2Ru{=}CHPh$, 15 mol%, **7a**:**7b**=7:1 (84%). (ii) NaH, THF, 65°C, 1 h, then allyl bromide, 65°C, 2 h (85%); (iii) $Cl_2(PCy_3)_2Ru{=}CHPh$, 5 mol% (83%).

fragment is observed, which is completely missing for the major isomer **7a** (Scheme 4).

What is the origin of the diastereoselectivity in the formation of **7**? To answer this question, we first investigated whether the five- or the six-membered ring is formed first. For this purpose, we conducted the ring closing metathesis of **4d** as an NMR-tube experiment in C_6D_6. After 1 h the starting material is nearly completely consumed, and a 1:1 mixture of the two diastereomeric dihydrofurans **9a,b** is formed. The second metathesis step is very slow and leads to the formation of the spirocycles in a 7:1 ratio of diastereomers. From these observations it may be concluded that **9a** cyclizes much faster than **9b**. Via a ring-opening/ring closing metathesis sequence[13] **9b** can be converted to **9a**, thereby restoring the equilibrium mixture. It was not possible to detect deviations from the 1:1 diastereomeric ratio of the intermediate **9** during the NMR-tube experiment, suggesting that the ring opening metathesis leading to equilibration is fast compared to the second ring closing metathesis step. No interconversion of **7a** into **7b** and vice versa was observed upon exposure to the Grubbs' catalyst, suggesting that ring closure of the six-membered ring is irreversible. The mechanistic proposal is summarized in Scheme 5.



Scheme 5. Proposed mechanism for the formation of **7a**,**b**.

In conclusion we have shown that diastereoselective ring closing metathesis leading to dihydropyrans with a 1,4-distance of the stereogenic centres can not be achieved by increasing the size of the substituents, whereas conformational rigidity, e.g. by incorporating one of the stereocentres into a cycle, may lead to stereodifferentiation. The formation of the dihydrofuran ring is fast and reversible by ring opening/ring closing metathesis, which allows an interconversion of the intermediates. Formation of the six-membered ring was found to be slow and irreversible. Application of this concept to the stereoselective synthesis of 2,5-difunctionalized dihydropyrans is currently under investigation.

Experimental

General remarks

All experiments were conducted in dry reaction vessels in an atmosphere of dry argon. Solvents were purified by standard procedures. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ with $CHCl_3$ as internal standard (δ=7.24). ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ with $CDCl_3$ as internal standard (δ=77.0). *J* values are given in Hz. The number of coupled protons was analysed by DEPT experiments and is denoted by a number in parentheses following the δ_C value. The NMR tube experiments were carried out in C_6D_6 at 500 MHz (^{1}H NMR). IR spectra were recorded as films on NaCl plates or as KBr disks. The peak intensities are defined as very strong (vs), strong (s), medium (m), and weak (w). Mass spectra were obtained at 70 eV. Alcohol **1** was prepared according to a literature procedure.[11] The ruthenium catalyst $Cl_2(PCy_3)_2Ru$=CHPh was prepared following Grubbs' procedure.[3]

[1-(4-Methoxyphenyl)-allyloxy]acetic acid ethyl ester (2). To a solution of alcohol **1** (3.28 g, 20 mmol) in THF (80 mL) was added NaH (1.44 g, 50% suspension in mineral oil, 30 mmol). The mixture was heated to reflux until the evolution of hydrogen gas finished, cooled to 0°C, and ethyl bromoacetate (3.33 mL, 30 mmol) in THF (20 mL) was added dropwise. After stirring at 0°C for 2 h the reaction was completed (TLC, hexanes/MTBE 5:1). Aqueous workup, followed by chromatography on silica (hexanes/MTBE 5:1), yielded 3.80 g (76%) of **2**. Anal.: Found: C, 67.0; H, 7.3, Calcd for $C_{14}H_{18}O_4$ C, 67.2; H, 7.3. LRMS (EI): *m*/*z* 250 (M^+, 28), 163 (100), 147 (51). ^{1}H NMR: δ 7.21 (d, 1, *J*=8.8 Hz, Ar), 6.80 (d, 1, *J*=8.8 Hz, Ar), 5.90 (ddd, 1, *J*=17.1 Hz, 10.3, 6.8, –CH=), 5.20 (dm, 1, *J*=17.1 Hz, CH_2), 5.15 (dm, 1, *J*=10.3 Hz, CH_2), 4.80 (d, 1, *J*=6.8 Hz, OCHAr), 4.12 (q, 2, *J*=7.0 Hz, OEt), 3.99 (d, 1, *J*=16.3 Hz, OCH*H*CO_2Et), 3.94 (d, 1, *J*=16.3 Hz, OCH*H*-CO_2Et), 3.71 (s, 3, OMe), 1.18 (t, 3, *J*=7.0 Hz, Et). ^{13}C NMR: δ 170.4 (0), 159.3 (0), 137.8 (1), 131.8 (0), 128.3 (1), 116.9 (2), 113.8 (1), 82.5 (1), 65.2 (2), 60.6 (2), 55.1 (3), 14.1 (3). IR (NaCl, neat) 2987 (w), 1753 (s), 1733 (s), 1611 (w), 1512 (s), 1248 (s), 1202 (s), 1118 (s), 1033 (s).

(*E*)-2-Hydroxy-5-(4-methoxyphenyl)-pent-4-enoic acid ethyl ester (3). To a solution of alcohol **1** (3.60 g, 22.0 mmol) in dry THF (50 mL) was added NaH (1.20 g, 60% dispersion in mineral oil, 30.0 mmol) and heated to reflux for 30 min. The mixture was cooled to 0°C and ethyl 2-bromoacetate was added. After 20 min at 0°C another portion of NaH (1.20 g, 60% dispersion in mineral oil, 30.0 mmol) was added and the mixture was stirred at room temperature for 2 h. After aqueous workup and chromatography α-hydroxy ester **3** was isolated in 2.15 g (38%) yield. LRMS (EI): *m*/*z* 250 (M^+, 10), 232 (10), 147 (100). ^{1}H NMR: δ 7.16 (d, 2, *J*=8.8 Hz, Ar), 6.72 (d, 1, *J*=8.8 Hz, Ar), 6.32 (d, 1, *J*=15.7, ArCH=), 5.95 (ddd, 1, *J*=15.7, 7.3, 7.3 Hz, ArCH=C*H*–), 4.23–4.07 (3, OCH*H*, C*H*OH), 3.68 (s, 3, OMe), 2.86 (d, 1, *J*=6.0 Hz, OH), 2.59 (dddd, 1, *J*=14.1 Hz, 7.3, 4.8, 1.5, CH*H*CH(OH)), 2.47 (dddd, 1, *J*=14.1, 7.3, 7.3, 1.3 Hz, CH*H*CH(OH)), 1.18 (t, 3, *J*=7.0 Hz, Et). ^{13}C NMR: δ 174.4 (0), 158.9 (0), 133.0 (1), 129.8 (0), 127.3 (1), 121.5 (1), 113.8 (1), 70.3 (1), 61.6 (2), 55.2 (3), 38.0 (2), 14.2 (3). IR (NaCl, neat) 3470 (s), 2982 (s), 2837 (m), 1739 (s), 1732 (s), 1608 (s), 1513 (s), 1250 (s), 1177 (s), 1032 (s), 969 (s), 839 (m).

1-[1-(4-Methoxyphenyl)allyloxy]-2-vinyl-but-3-en-2-ol (4a). A solution of vinyl–magnesium chloride in THF (23.0 mL, 1.7 M, 40.0 mmol) was added dropwise at −60°C to a solution of the ester **3** (3.20 g, 12.8 mmol) in ether (100 mL). The mixture was stirred for 1 h, then warmed to room temperature and stirring was continued for 2 h. The reaction was poured onto aqueous NH_4Cl solution (50 mL), the aqueous layer was separated and extracted with MTBE; the combined organic layers were dried with $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica using hexanes/MTBE mixtures of increasing polarity as eluent. Yield: 1.70 g (52%). Anal.: Found: C, 73.9; H, 7.7, Calcd for $C_{16}H_{20}O_3$ C, 73.8; H, 7.7. LRMS (EI): *m*/*z* M^+ not observed, 147 (100). ^{1}H NMR: δ 7.21 (d, 2, *J*=8.8 Hz, Ar), 6.86 (d, 2, *J*=8.8 Hz, Ar), 5.93–5.86 (3, –C*H*=CH_2), 5.35 (dd, 1, *J*=17.3, 1.4 Hz, –CH=C*H*$_2$), 5.32 (dd, 1, *J*=17.3, 1.4 Hz, –CH=C*H*$_2$), 5.22 (ddd, 1, *J*=17.3, 1.5, 1.5 Hz, CHCH=C*H*$_2$), 5.18–5.15 (3, –CH=C*H*$_2$), 4.72 (d, 1, *J*=6.5 Hz, ArC*H*O), 3.78 (s, 3, OMe), 3.43 (d, 1, *J*=9.2 Hz, OCH*H*), 3.34 (d, 1, *J*=9.2 Hz, OCH*H*). ^{13}C NMR: δ 159.2 (0), 139.8 (1), 139.7 (1), 138.6 (1), 132.6 (0), 128.1 (1), 116.1 (2), 114.7 (2), 114.7 (2), 113.8 (1),

83.1 (1), 75.4 (0), 74.1 (2), 55.2 (3). IR (NaCl, neat) 3555 (m), 2934 (m), 1610 (s), 1512 (s), 1088 (s), 926 (s), 831 (m).

1-[1-(4-Methoxyphenyl)allyloxy]-hex-5-en-2-one (5). Colourless liquid, separated from the triene **10a** by column chromatography. Yield: 0.31 g (9%). LRMS (EI): *m*/*z* M^+ not observed, 147 (100). ^{1}H NMR: δ 7.23 (d, 2, *J*=8.8 Hz, Ar), 6.85 (d, 2, *J*=8.8 Hz, Ar), 5.92 (ddd, 1, *J*=17.1 Hz, 10.3, 6.5, –CHC*H*=CH$_2$), 5.76 (dddd, 1, *J*=17.0, 10.0, 6.4, 6.4 Hz, –CH$_2$C*H*=CH$_2$), 5.25 (d, 1, *J*=17.1 Hz, CH=C*H*$_2$), 5.19 (d, 1, *J*=10.3 Hz, CH=CH$_2$), 4.99 (dm, 1, *J*=17.0 Hz, CH=CH$_2$), 4.93 (dm, 1, *J*=10.0, CH=CH$_2$), 4.72 (d, 1, *J*=6.5 Hz, ArC*H*O), 3.98 (d, 1, *J*=17.0 Hz, OCH*H*C=O), 3.92 (d, 1, *J*=17.0 Hz, OCH*H*C=O), 3.76 (s, 3, OMe), 2.58–2.53 (2, CH*H*), 2.33–2.25 (2, CH*H*). ^{13}C NMR: δ 208.4 (0), 159.3 (0), 138.0 (1), 136.9 (1), 131.9 (0), 128.2 (1), 116.7 (2), 115.3 (2), 113.9 (1), 82.8 (1), 73.3 (2), 55.2 (3), 38.2 (2), 27.1 (2). IR (NaCl, neat) 3078 (m), 2934 (m), 1720 (s), 1611 (s), 1512 (s), 1248 (s), 1105 (s), 1035 (s), 919 (s).

1-[1-(2-Benzyloxy-2-vinyl-but-3-enyloxy)-allyl]-4-methoxybenzene (4b). To a solution of **4a** (0.30 g, 1.2 mmol) in THF (10 mL) was added NaH (160 mg, 60% dispersion in mineral oil, 4.0 mmol). The mixture was refluxed for 30 min, and then benzyl bromide (0.50 mL, 4.2 mmol) was added, and the mixture was again refluxed, until the starting material was completely consumed as indicated by TLC (hexanes/MTBE 10:1). The reaction was quenched by addition of water (10 mL). The mixture was extracted with MTBE and dried over $MgSO_4$. Evaporation of the solvent and flash chromatography yields 0.37 g (88%) of **4b**. Anal.: Found: C, 78.0; H, 7.4, Calcd for $C_{23}H_{26}O_3$ C, 78.8; H, 7.5. LRMS (EI): *m*/*z* (M^+ not observed), 162 (30), 147 (100), 91 (54). ^{1}H NMR: δ 7.33–7.12 (7, Ar, Ph), 6.82 (d, 2, *J*=8.8 Hz, Ar), 5.97 (dd, 1, *J*=17.5, 10.5 Hz, –C*H*=CH$_2$), 5.95 (dd, *J*=17.5, 10.5 Hz, –C*H*CH$_2$), 5.86 (ddd, 1, *J*=17.1, 10.3, 6.3 Hz, CHC*H*=CH$_2$), 5.34 (dd, 1, *J*=17.5, 1.5 Hz, –CH=C*H*$_2$), 5.33 (dd, 1, *J*=17.5, 1.5 Hz, –CH=C*H*$_2$), 5.30 (dd, 1, *J*=10.5, 1.5 Hz, –CH=C*H*$_2$), 5.28 (dd, 1, *J*=10.5, 1.5 Hz, –CH=C*H*$_2$), 5.21 (ddd, 1, *J*=17.1, 1.5, 1.5 Hz, –CHCH=C*H*$_2$), 5.12 (ddd, 1, *J*=10.3, 1.5, 1.5 Hz, –CHCH=C*H*$_2$), 4.74 (d, 1, *J*=6.3 Hz, ArC*H*O), 4.46–4.44 (2, OC*HH*Ph), 3.74 (s, 3, OMe), 3.55 (d, 1, *J*=10.0 Hz, OCH*H*), 3.47 (d, 1, *J*=10.0, OCH*H*). ^{13}C NMR: δ 1159.0 (0), 139.6 (0), 139.0 (1), 137.9 (1), 137.9 (1), 133.1 (0), 128.1 (1), 128.1 (1), 127.1 (1), 127.0 (1), 117.1 (2), 117.1 (2), 115.8 (2), 113.7 (1), 83.0 (1), 80.7 (0), 73.8 (2), 65.5 (2), 55.2 (3). IR (NaCl, neat) 3029 (m), 2951 (m), 2933 (m), 1610 (s), 1511 (s), 1248 (s), 1089 (s), 929 (s).

***tert*-Butyl-{1-[1-(4-methoxyphenyl)-allyloxymethyl]-1-vinylallyloxy}-dimethylsilane (4c). 4c** was obtained from triene **4a** (0.44 g, 1.7 mmol) and *tert*-butyldimethylsilyl chloride (0.75 g, 5.1 mmol) following the procedure given above for the preparation of **4b** (TLC: hexanes/MTBE 50:1). Yield: 0.54 g (86%). LRMS (EI): *m*/*z* 374 (M^+, <1%), 259 (6%, M^+-TBDMS), 147 (100). ^{1}H NMR: δ 7.23 (d, 2, *J*=8.5 Hz, Ar), 6.87 (d, 2, *J*=8.5 Hz, Ar), 6.03 (dd, 1, *J*=17.3, 10.5 Hz, –C*H*=CH$_2$), 5.96 (dd, *J*=17.3, 10.5 Hz, –C*H*=CH$_2$), 5.90 (ddd, 1, *J*=17.1, 10.3, 6.5 Hz, CHC*H*=CH$_2$), 5.32 (ddd, 1, *J*=17.3, 1.3, 1.3 Hz, –CHCH=C*H*$_2$), 5.23 (ddd, 1, *J*=10.3, 1.3, 1.3 Hz, –CHCH=C*H*$_2$), 5.18–5.12 (4, –CH=C*H*$_2$), 4.70 (d, 1, *J*=6.5 Hz, OC*H*CH=CH$_2$), 3.40 (d, 1, *J*=9.3 Hz, OCH*H*), 3.31 (d, 1, *J*=9.3 Hz, OCH*H*), 3.79 (s, 3, OMe), 0.89 (s, 9, *tert*-Bu), 0.06 (s, 3, Si(C*H*$_3$)$_2$), 0.05 (s, 3, Si(C*H*$_3$)$_2$). ^{13}C NMR: δ 159.0 (0), 140.9 (1), 140.8 (1), 139.2 (1), 133.1 (0), 128.1 (1), 115.7 (2), 114.8 (2), 114.8 (2), 113.7 (1), 83.2 (1), 77.8 (0), 75.2 (2), 55.2 (3), 26.0 (3), 18.5 (0), 2.1 (3), 2.1 (3). IR (NaCl, neat) 2956 (m), 2929 (m), 2856 (m), 1511 (s), 1249 (s), 1093 (m), 1040 (m), 836 (m), 776 (m).

1-[1-(2-Allyloxy-2-vinyl-but-3-enyloxy)-allyl]-4-methoxybenzene (4d). 4d was obtained from triene **4a** (0.83 g, 3.2 mmol) and allyl bromide (0.43 mL, 5.0 mmol) following the procedure given above for the preparation of **4b** (TLC: hexanes/MTBE 10:1). Yield: 0.75 g (78%). LRMS (EI): *m*/*z* M^+ not observed, 147 (100). ^{1}H NMR: δ 7.21 (d, 2, *J*=8.5 Hz, Ar), 6.83 (d, 2, *J*=8.5 Hz, Ar), 5.96–5.82 (4, –C*H*=CH$_2$), 5.32–5.22 (5, –CH=C*H*$_2$), 5.20 (ddd, 1, *J*=17.1, 1.4, 1.4 Hz, –CH=C*H*$_2$), 5.12 (dm, 1, *J*=10.3 Hz, –CH=C*H*$_2$), 5.07 (dddd, 1, *J*=10.3, 1.5, 1.5, 1.5 Hz, –CH=C*H*$_2$), 4.73 (d, 1, *J*=6.5 Hz, OC*H*CH=CH$_2$), 3.91 (ddd, 2, *J*=5.3, 1.5, 1.5 Hz, OC*HH*CH=CH$_2$), 3.76 (s, 3, OMe), 3.49 (d, 1, *J*=9.8 Hz, OCH*H*), 3.41 (d, 1, *J*=9.8 Hz, OCH*H*). ^{13}C NMR: δ 159.0 (0), 139.0 (1), 137.9 (1), 137.9 (1), 135.8 (1), 133.1 (0), 128.1 (1), 116.9 (2), 116.8 (2), 115.8 (2), 115. 5 (2), 113.7 (1), 83.0 (1), 80.6 (0), 73.8 (2), 64.7 (2), 55.2 (3). IR (NaCl, neat) 3082 (m), 2909 (m), 1836 (m), 1611 (s), 1511 (s), 1105 (s), 925 (s), 829 (s).

(3*R 6*S**-6-(4-methoxyphenyl)-3-vinyl-3,6-dihydro-2*H*-pyran-3-ol (*cis*-6a) and (3*R** 6*R**)-6-(4-methoxyphenyl)-3-vinyl-3,6-dihydro-2*H*-pyran-3-ol (*trans*-6a).** To a solution of the triene **4a** (0.34 g, 1.3 mmol) in DCM (15 mL) was added the Grubbs' catalyst (0.075 g, 7 mol%) and the mixture was stirred at ambient temperature for 24 h leading to a 2:3 mixture of diastereomers. Evaporation of the solvent followed by column chromatography on silica (hexanes/MTBE mixtures of increasing polarity) gave the diastereoisomers in 84% yield. Diastereomer *cis*-**6a**: colourless liquid, 0.10 g. Anal.: Found: C, 72.2; H, 6.9, Calcd for $C_{14}H_{16}O_3$ C, 72.4; H, 6.9. LRMS (EI): *m*/*z* 232 (M^+, 5%), 215 (100), 202 (30), 121 (40). ^{1}H NMR: δ 7.28 (d, 2, *J*=8.8, Ar), 6.88 (d, 2, *J*=8.8 Hz, Ar), 5.95 (d, 1, *J*=10.5 Hz, H3), 5.92 (dd, 1, *J*=10.5, 1.0 Hz, H4), 5.88 (dd, 1, *J*=17.3 Hz, 10.8, CHC*H*=CH$_2$), 5.41 (dd, 1, *J*=17.3, 1.3 Hz, CH=C*H*$_2$), 5.24 (d, 1, *J*=10.8, 1.3 Hz, CH=C*H*$_2$), 5.00 (s (br), 1, H2), 3.86 (dd, 1, *J*=11.5, 1.0 Hz, H6), 3.78 (s, 3, OMe), 3.68 (d, 1, *J*=11.5 Hz, H6), 2.46 (s, 1, OH). ^{13}C NMR: δ 159.6 (0), 138.7 (1), 131.9 (0), 131.8 (1), 130.1 (1), 128.7 (1), 115.8 (2), 114.0 (1), 76.4 (1), 74.2 (2), 68.0 (0), 55.3 (3). IR (NaCl, neat) 3427 (s br), 2959 (m), 1611 (s), 1514 (s), 1247 (s), 1175 (s), 1080 (s), 821 (s). Diastereomer *trans*-**6a**: colourless liquid, 0.16 g. LRMS (EI): *m*/*z* 232 (M^+, 5%), 215 (50), 202 (60), 121 (100). ^{1}H NMR: δ 7.19 (d, 2, *J*=8.8 Hz, Ar), 6.82 (d, 2, *J*=8.8 Hz, Ar), 5.95 (dd, 1, *J*=17.3, 10.8, C*H*=CH$_2$), 5.90 (dd, 1, *J*=10.3, 2.0 Hz, H3,4), 5.82 (dd, 1, *J*=10.3, 1.8 Hz, H3,4), 5.33 (dd, 1, *J*=17.3, 0.8 Hz, CH=C*H*$_2$), 5.16 (d, 1, *J*=10.8, 0.8 Hz, CH=C*H*$_2$), 5.06 (dd, 1, *J*=2.0, 1.8 Hz, H2), 3.73 (s, 3, OMe), 3.69 (d, 1, *J*=11.3 Hz, H6), 3.54 (d, 1, *J*=11.3 Hz,

H6), 2.21 (s, 1, OH). ^{13}C NMR: δ 159.5 (0), 140.1 (1), 131.4 (0), 130.4 (1), 130.3 (1), 129.2 (1), 115.0 (2), 113.9 (1), 75.1 (1), 71.4 (2), 68.5 (0), 55.3 (3). IR (NaCl, neat) 3418 (s br), 2958 (s), 1611 (s), 1513 (s), 1247 (s), 1174 (s), 1085 (s), 1035 (s), 732 (s).

3-Benzyloxy-6-(4-methoxyphenyl)-3-vinyl-3,6-dihydro-2*H*-pyran (6b). 6b was obtained from triene **4b** (0.16 g, 0.4 mmol) and the Grubbs' catalyst (0.026 g, 7 mol%) following the procedure given above for the preparation of dihydropyrans **6a** as an inseparable 1:1 mixture of diastereoisomers. Yield: 0.12 g (81%). LRMS (EI): *m*/*z* M^+ not observed. ^{1}H NMR: δ 7.38–7.10 (7, Ar, Ph), 6.88–6.82 (2, Ar), 6.13–5.83 (3, –C*H*═CH_2, H3,4), 5.42 (dd, 1, *J*=17.5, 1.3 Hz, –CH═CH_2), 5.37 (dd, 1, *J*=17.5, 1.3 Hz, –CH═CH_2), 5.33 (dd, *J*=10.6, 1.5 Hz, –CHCH_2), 5.26 (dd, 1, *J*=10.3, 1.5 Hz, –CH═CH_2), 5.07 (s, 1, H2), 4.98 (s, 1, H2), 4.71 (d, 1, *J*=11.5 Hz, OCH*H*Ph), 4.64 (d, 1, *J*=11.5 Hz, OCH*H*Ph), 4.61 (d, 1, *J*=11.6 Hz, OCH*H*Ph), 4.56 (d, 1, *J*=11.6 Hz, OCH*H*Ph), 4.12 (dd, 1, *J*=12.2, 1.0 Hz, H6), 3.88 (d, 1, *J*=11.3 Hz, H6), 3.83 (d, 1, *J*=11.3 Hz, H6), 3.75 (s, 3, OMe), 3.68 (d, 1, *J*=12.2 Hz, H6). ^{13}C NMR: δ 159.5 (0), 159.5 (0), 139.9 (1), 139.5 (0), 139.3 (1), 139.2 (0), 134.2 (1), 132.3 (1), 132.2 (0), 131.9 (0), 129.0 (1), 128.8 (1), 128.4 (1), 128.1 (1), 127.5 (1), 127.3 (1), 127.2 (1), 127.1 (1), 127.1 (1), 126.6 (1), 117.3 (2), 116.5 (2), 113.9 (1), 113.8 (1), 76.0 (1), 75.8 (1), 73.5 (0), 72.6 (0), 72.5 (2), 70.3 (2), 66.3 (2), 65.3 (2), 55.2 (3), 55.2 (3). IR (NaCl, neat) 1611 (m), 1513 (s), 1248 (s), 1093 (s), 1035 (m), 829 (m), 734 (m).

***tert*-Butyl-[6-(4-methoxyphenyl)-3-vinyl-3,6-dihydro-2*H*-pyran-yloxy]-dimethyl-silane (6c). 6c** was obtained from triene **4c** (0.15 g, 0.4 mmol) and the Grubbs' catalyst (0.033 g, 10 mol%) following the procedure given above for the preparation of dihydropyrans **6a** as an inseparable 2:1 mixture of diastereoisomers. Yield: 0.11 g (80%). LRMS (EI): *m*/*z* 346 (M^+, 1%), 289 (M^+-*tert*-Bu, 39), 121 (100). IR (NaCl, neat) 2956 (m), 2929 (m), 2856 (m), 1611 (m), 1511 (s), 1249 (s), 1106 (s), 1040 (m), 836 (m), 776 (m). NMR-data of the major isomer *cis*-**6c**: ^{1}H NMR: δ 7.27 (d, 2, *J*=8.8 Hz, Ar), 6.89 (d, 2, *J*=8.8 Hz, Ar), 6.06 (dd, 1, *J*=17.2 Hz, 10.5, –C*H*═CH_2), 5.87 (dd, 1, *J*=10.2, 1.3 Hz, H3,4), 5.83 (ddd, 1, *J*=10.2, 1.7, 1.3 Hz, H3,4), 5.38 (dd, 1, *J*=17.2, 1.5 Hz, –CH═CH_2), 5.17 (dd, 1, *J*=10.5, 1.5 Hz, –CH═CH_2), 5.08 (s, 1, H2), 3.80 (s, 3, OMe), 3.81–3.79 (1, H6 overlapped by OMe), 3.67 (d, 1, *J*=10.7 Hz, $H6_{ax}$), 0.91 (s, 9, *tert*-Bu), 0.16 (s, 3, Si(CH_3)$_2$), 0.15 (s, 3, Si(CH_3)$_2$). ^{13}C NMR: δ 159.4 (0), 142.3 (1), 132.3 (0), 130.9 (1), 129.8 (1), 128.8 (1), 114.0 (2), 113.8 (1), 76.0 (1), 73.0 (2), 71.0 (0), 55.2 (3), 25.8 (3), 18.2 (0), 2.2 (3), 2.3 (3). NMR-data of the minor isomer *trans*-**6c**: ^{1}H NMR: δ 7.34 (d, 2, *J*=8.7 Hz, Ar), 6.91 (d, 2, *J*=8.7 Hz, Ar), 5.99 (dd, 1, *J*=10.2, 2.0 Hz, H3), 5.92 (dd, 1, *J*=17.0, 10.5 Hz, –C*H*═CH_2), 5.88 (dd, 1, *J*=10.2, 2.0 Hz, H4), 5.36 (dd, 1, *J*=17.2, 1.5 Hz, –CH═CH_2), 5.17 (dd, 1, *J*=10.5, 1.5 Hz, –CH═CH_2), 5.01 (dd, 1, *J*=2.0, 2.0 Hz, H2), 3.82 (s, 3, OMe), 3.81–3.79 (1, H6 overlapped by OMe), 3.36 (d, 1, *J*=11.5 Hz, $H6_{ax}$), 0.91 (s, 9, *tert*-Bu), 0.13 (s, 3, Si(CH_3)$_2$), 0.11 (s, 3, Si(CH_3)$_2$). ^{13}C NMR: δ 159.3 (0), 141.8 (1), 132.2 (0), 130.7 (1), 130.3 (1), 128.8 (1), 114.3 (2), 113.7 (1), 75.3 (1), 73.1 (2), 70.6 (0), 55.2 (3), 25.8 (3), 18.2 (0), 2.2 (3), 2.3 (3).

(3*R, 6*R**)-3-Allyloxy-6-(4-methoxyphenyl)-3-vinyl-3,6-dihydro-2*H*-pyran (8). 8** was obtained from *cis*-**6a** (0.20 g, 0.8 mmol) and allyl bromide (0.20 mL, 2.4 mmol) following the procedure given above for the preparation of **4b**–**d** (TLC: hexanes/MTBE 10:1). Yield: 0.20 g (85%). LRMS (EI): *m*/*z* 272 (M^+, 12%), 242 (43), 201 (77), 135 (49), 55 (100). ^{1}H NMR: δ 7.31 (d, 2, *J*=8.5 Hz, Ar), 6.88 (d, 2, *J*=8.5 Hz, Ar), 6.10 (dd, 1, *J*=10.3, 1.5 Hz, H3,4), 5.96 (dddd, 1, *J*=17.2, 10.5, 5.3, 5.3 Hz, OCHHC*H*═CH_2), 5.88 (dm, 1, *J*=10.3 Hz, H3,4), 5.84 (dd, 1, *J*=17.6 Hz, 10.8, C*H*═CH_2), 5.37 (dd, 1, *J*=17.6, 0.8 Hz, CH═CH_2), 5.30 (dddd, 1, *J*=17.2, 1.8, 1.8, 1.8 Hz, OCHHCH═CH_2), 5.26 (d, 1, *J*=10.8 Hz, 0.8, CH═CH_2), 5.13 (dddd, 1, *J*=10.3 Hz, 1.8, 1.8, 1.8, OCHHCH═CH_2), 4.98 (s, 1, H2), 4.20 (ddm, 1, *J*=12.6, 5.3 Hz, OCH*H*CH═CH_2), 4.11 (ddm, 1, *J*=12.6, 5.3 Hz, OCH*H*CH═CH_2), 4.05 (d, 1, *J*=12.0 Hz, H6), 3.78 (s, 3, OMe), 3.65 (d, 1, *J*=12.0 Hz, H6). ^{13}C NMR: δ 159.4 (0), 139.3 (1), 135.8 (1), 134.0 (1), 132.2 (0), 128.8 (1), 126.6 (1), 116.4 (2), 115.9 (2), 113.9 (1), 75.9 (1), 72.4 (0), 72.3 (2), 65.3 (2), 55.2 (3). IR (NaCl, neat) 2958 (m), 2838 (m), 1612 (s), 1514 (s), 1249 (s), 1173 (m), 1089 (s), 1036 (m), 926 (m).

(5*R, 8*S**)-8-(4-Methoxyphenyl)-1,7-dioxaspiro[4,5]deca-3,9-diene (7a).** To a solution of the tetraene (0.30 g, 1.0 mmol) in toluene (15 mL) was added the Grubbs' catalyst (0.123 g, 15 mol%). The mixture was heated to reflux for 18 h, the solvent was evaporated and the residue purified by column chromatography to give **7a** (0.18 g, 72%) along with the (5*S**, 8*S**)-diastereoisomer **7b** (0.03 g, 12%). LRMS (EI): *m*/*z* 245 (M^++1, 10%), 214 (100), 121 (50). ^{1}H NMR (C_6D_6): δ 7.26 (d, 2, *J*=8.8 Hz, Ar), 6.82 (d, 2, *J*=8.8 Hz, Ar), 5.88 (ddd, 1, *J*=5.9, 2.0, 2.0 Hz, H4′), 5.87 (dm, *J*=10.3 Hz, H4), 5.66 (dd, 1, *J*=10.3, 2.0 Hz, H3), 5.45 (ddd, 1, *J*=5.9, 2.0, 2.0 Hz, H3′), 4.97 (dd, 1, *J*=2.0, 2.0 Hz, H2), 4.51 (ddd, 1, *J*=13.0, 2.0, 2.0 Hz, H5′), 4.42 (ddd, 1, *J*=13.0, 2.0, 2.0 Hz, H5′), 4.01 (d, 1, *J*=10.8 Hz, $H6_{eq}$), 3.97 (d, 1, *J*=10.8 Hz, $H6_{ax}$), 3.32 (s, 3, OMe). ^{13}C NMR (C_6D_6): δ 159.9 (0, *C*OMe), 133.4 (0, *ipso*C), 131.8 (1, C4′), 130.6 (1, C3), 129.9 (1, C4), 129.0 (1, Ar), 127.0 (1, C3′), 114.1 (1, Ar), 84.9 (0, C5), 76.2 (1, C2), 74.8 (2, C5′), 72.5 (2, C6), 54.7 (3, OMe). IR (NaCl, neat) 2960 (m), 2853 (m), 1610 (m), 1513 (s), 1249 (s), 1080 (s), 1033 (s), 829 (m).

(5*R, 8*R**)-8-(4-Methoxyphenyl)-1,7-dioxaspiro[4,5]deca-3,9-diene (7b).** To a solution of the dihydropyran **8** (0.15 g, 0.6 mmol) in DCM (15 mL) was added the Grubbs' catalyst (0.025 g, 5 mol%). The mixture was stirred at ambient temperature for 24 h. The solvent was evaporated and the residue purified by column chromatography to give **7b** (0.12 g, 83%). LRMS (EI): *m*/*z* 245 (M^++1, 15), 214 (100), 121 (35). ^{1}H NMR: δ 7.31 (d, 2, *J*=8.5 Hz, Ar), 6.85 (d, 2, *J*=8.5 Hz, Ar), 6.03 (dm, 1, *J*=6.3 Hz, H4′), 5.93 (dd, *J*=10.3, 1.8 Hz, H3), 5.82 (dm, 1, *J*=10.3 Hz, H4), 5.67 (ddd, 1, *J*=6.3, 2.8, 2.3 Hz, H3′), 4.97 (s, 1, H2), 4.75 (ddd, 1, *J*=13.1, 2.0, 2.0 Hz, H5′), 4.67 (dm, 1, *J*=13.0 Hz, H5′), 3.87 (d, 1, *J*=11.8 Hz, $H6_{eq}$), 3.76 (s, 3, OMe), 3.63 (d, 1, *J*=11.8 Hz, $H6_{ax}$). ^{13}C NMR: δ 159.3 (0, *C*OMe), 132.2 (1, C3), 132.1 (0, *ipso*C), 129.4 (1, C3′), 129.2 (1, C4′), 128.9 (1, Ar), 127.8 (1, C4), 113.7 (1, Ar), 83.9 (0, C5), 75.3 (1, C2), 74.6 (2, C5′), 70.3 (2, C6), 55.2

(3, OMe). IR (KBr, neat) 2956 (m), 2838 (s), 1612 (s), 1513 (s), 1248 (s), 1075 (s), 1034 (s), 831 (s), 810 (s).

NMR-tube experiment

RCM of tetraene 10d. Tetraene **10d** (28 mg) was dissolved in C_6D_6 (1.0 mL) in an NMR tube under an argon atmosphere. The Grubbs' catalyst (8 mg) was added and ^{1}H NMR spectra were recorded at 500 MHz after 10, 45, 70, 100 min, 10 and 48 h. NMR data of **2-[1-(4-methoxyphenyl)-allyloxymethyl]-2-vinyl-2,5-dihydrofuran (9)** (1:1 mixture of diastereomers): ^{1}H NMR (C_6D_6): δ 7.28 (d, 2, J=8.8 Hz, Ar), 7.27 (d, 2, J=8.8 Hz, Ar), 6.81 (d, 2, J=8.8 Hz, Ar), 6.81 (d, 2, J=8.8 Hz, Ar), 6.18 (dd, 1, J=17.3, 10.8 Hz, –C*H*CH$_2$), 6.10 (dd, 1, J=17.3, 10.8 Hz, –C*H*CH$_2$), 6.00–5.89 (2, CHC*H*=CH$_2$), 5.79–5.75 (2, –*H*C=C*H*), 5.55–5.44 (4, –*H*C=C*H*–+=C*H*$_2$), 5.27 (ddd, 1, J=17.3, 1.5, 1.5 Hz, =CH$_2$), 5.25 (ddd, 1, J=17.3, 1.5, 1.5 Hz, =CH$_2$), 5.12 (dd, 1, J=10.8, 2.0, =CH$_2$), 5.08 (dd, 1, J=10.8, 2.0 Hz, =CH$_2$), 5.08–5.03 (2, =CH$_2$), 4.75–4.70 (2, OCHAr), 4.65–4.47 (2, OC*HH*CH=), 3.62–3.50 (2, OC*HH*C$_q$), 3.32 (s, 3, OMe). ^{13}C NMR (C_6D_6): δ 159.7 (0), 159.6 (0), 139.9 (1), 139.9 (1), 139.7 (1), 139.6 (1), 133.6 (0), 133.5 (0), 130.4 (1), 130.4 (1), 128.5 (1), 128.4 (1), 126.9 (1), 126.9 (1), 115.3 (2), 115.1 (2), 114.1 (1), 114.1 (1), 113.7 (2), 113.7 82), 92.4 (0), 92.4 (0), 83.2 (1), 83.2 (1), 75.3 (2), 75.3 (2), 74.2 (2), 74.1 (2), 54.7 (3), 54.7 (3).

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