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A Short Olefin Metathesis-Based Route to Enantiomerically Pure Arylated Dihydropyrans and α,β-Unsaturated δ-Valero Lactones

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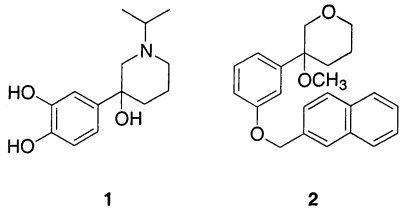
The synthesis of arylated dihydropyrans and unsaturated lactones starting from enantiomerically pure α-hydroxy ketones (prepared by an enzyme-catalyzed benzoin condensation) is described. The key steps are a highly diastereoselective addition of vinyl metal compounds under chelate control and a ruthenium-catalyzed ring-closing olefin metathesis reaction. Elucidation of the relative configuration of the final products was achieved by NOE experiments.

Arylated heterocycles have been a synthetic target in several pharmaceutical research laboratories. Potential applications range from 5-Lipoxygenase inhibitors[1] to NK-1 receptor antagonists[2,3] and ligands for receptors of neurotransmitters.[4,5] Methods for the introduction of aryl moieties to heterocycles include Heck reactions[2] or Stille couplings,[3] asymmetric Michael reactions of aryl acetic acids,[6] and addition of aryl metal compounds to heterocycloalkanones. Two examples of biologically active heterocycles synthesized by this method are depicted in Figure 1: the piperidine **1** shows adrenoceptor agonist activity,[7] while the tetrahydropyran **2** inhibits leukotriene synthesis in vitro.[1]

The structural pattern present in **2** inspired a short and highly diastereoselective synthesis of more densely functionalized enantiomerically pure analogues. Our synthetic concept is based on the ring-closing olefin metathesis reaction[8−11] and uses enantiomerically pure α-hydroxy-aryl ketones **3** as starting materials. The ketones **3** were obtained on a preparative scale in high chemical and optical yield by benzaldehyde lyase (BAL)-catalyzed benzoin condensation-like reaction from aromatic aldehydes and acetaldehyde.[12,13] Using this thiamine diphosphate (ThDP)-dependent enzyme in an aqueous buffer solution a large number of highly enantioenriched (*R*)-benzoins and (*R*)-2-hydroxy-1-phenyl-1-propanones substituted in ortho-, meta-, and para-positions by diverse moieties are available in one reaction step. Additionally, direct access to the corresponding (*S*)-enantiomers is also given by using the same enzymes' racemic resolution ability or by using other ThDP-dependent enzymes.[14,15]



1 2

FIGURE 1. Examples for biologically active, arylated heterocycles.

Following the sequence outlined in Scheme 1, dihydropyrans **7a**−**e** were obtained as single diastereomers in enantiomerically pure form.

Starting from α-hydroxy ketones **3**, allyloxy ketones **4** were obtained using silver oxide and allyl bromide.[16] By using this method, racemization at the α-carbon was avoided and allyl ethers **4** were obtained in an enantio-

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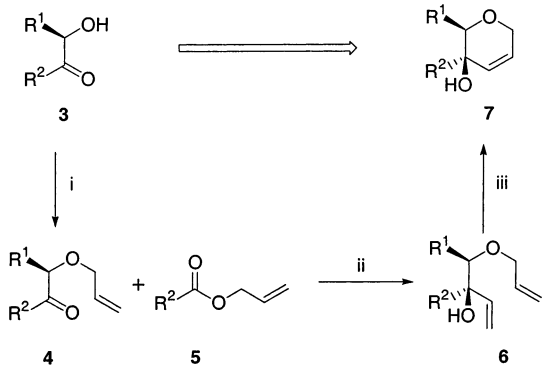
SCHEME 1[a]



[a] Reagents and conditions: (i) Ag_2O (1.5 equiv), $H_2C{=}CHCH_2Br$, ether, 20 °C; (ii) $H_2C{=}CHMgCl$, ether, −78 °C; (iii) $Cl_2(Cy_3P)_2Ru{=}CHPh$ (A) (3 mol %), CH_2Cl_2, 20 °C.

TABLE 1. Synthesis of Arylated Dihydropyrans

compd	R^1	R^2	% yield of **4**	**4**:**5**	% yield of **6** (dr)	% yield of **7**
(*R*)-**3a**	Ph	Ph	90	10:1	99 (>19:1)	90
(*R*)-**3b**	Me	Ph	47	1:1	67 (>19:1)	86
(*S*)-**3b**	Me	Ph	47	1:1	62 (>19:1)	80
(*R*)-**3c**	3-OMe-Ph	3-OMe-Ph	99	>19:1	79 (>19:1)	90
(*R*)-**3d**	2-Cl-Ph	2-Cl-Ph	75	5:1	85 (>19:1)	75
(*R*)-**3e**	4-Br-Ph	4-Br-Ph	73	5:1	90 (>19:1)	78

merically pure form. If strong bases, such as NaH, are used, an *O*-allylation-Wittig rearrangement takes place, leading to aryl-allyl carbinols.[17] In the case of (*R*)- and (*S*)-**3b**, allyl benzoate was formed as an inseparable byproduct. Obviously, oxidative cleavage of the acyloin linkage occurs, leading to benzoic acid, which is then allylated to give the corresponding allyl ester. In all other cases, only minor amounts of allyl esters **5** result. The amount of **5** increases with an increasing amount of silver oxide, thus, a large excess of silver oxide should be carefully avoided. By treatment of the α-allyloxy ketones **4** with vinylmagnesium chloride in THF/ether at low temperature, the dienes **6** were obtained with very high diastereoselectivity. In all cases investigated, only one diastereomer could be detected in the proton NMR spectrum of the crude reaction mixture, corresponding to a diastereomeric ratio higher than 19:1. For **6a** we proved that the vinylation reaction occurs without any racemization. Racemic **6a** was prepared from commercial benzoin and compared with material obtained via the same sequence from (*R*)-**3a** using HPLC on chirally modified stationary phases. The amount of the *S*-enantiomer was below the detection limit corresponding to an enanantiomeric excess of >99%. Ring-closing metathesis of the dienes **6** to the dihydropyrans **7** proceeded smoothly in the presence of 3 mol % of the first generation Grubbs' catalyst (**A** in Figure 2). Only **6d** required 10 mol % of the ruthenium catalyst for complete conversion to the dihydropyran **7d**. The significantly reduced reactivity of **6d** might be explained by steric interactions of the substituent in the ortho-position of the aromatic ring with the ligand sphere of the ruthenium complex. As a consequence, conformations suitable for ring closure

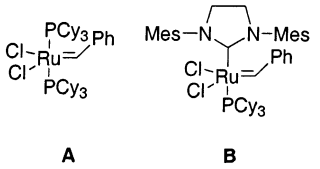


FIGURE 2. First (**A**) and second (**B**) generation Grubbs' catalyst.

become higher in energy compared to derivatives not substituted in the ortho-position.

Modification of the sequence outlined above allows the conversion of α-hydroxy ketones to α,*β*-unsaturated lactones **10**. Starting from **3c**,**f**, vinylation to the corresponding diol **8c**,**f** is achieved by addition of excess vinylmagnesium chloride. Again, HPLC on chirally modified stationary phases proved that no racemization occurs on this step. For this purpose, racemic **8c** was prepared from the corresponding racemic benzoin and compared with material obtained from enantiomerically pure (*R*)-**3c**. In this case a small amount of the *S*-enantiomer was observed (ee of (*R*)-**8c**: 98%). The diols **8c**,**f** were converted to the acrylates **9c**,**f** by reaction with acryloyl chloride. Competitive esterification of the tertiary alcohol was not observed if a large excess of base and acryloyl chloride was avoided and if the reaction was quenched immediately after consumption of the starting material (TLC control). Conversion of the sterically more hindered substrate **8c** to **9c** requires longer reaction times and the addition of a catalytic amount of DMAP. **8f** is readily converted to **9f** without additives.

Ring-closing metathesis of dienes containing one electron-deficient double bond with the first generation catalyst **A** is normally not a facile process due to the inhibition of the catalytically active species by chelation. This problem may be circumvented by addition of a Lewis acid,[18] or by using the second generation catalyst **B**.[19] We chose the latter option for converting dienes **9c**,**f** to the corresponding lactones **10c**,**f**. In the presence of 4 mol % of **B** complete conversion was achieved within 30 min at 70 °C. Over the past three years some examples of the formation of α,*β*-unsaturated lactones by olefin metathesis of acrylates using complex **B** have been described in the literature.[20−23] Nevertheless, it is surprising that ring closure of the sterically demanding *and* electron-deficient dienes **9** is such a smooth process. The results are summarized in Scheme 2 and Table 2.

The relative stereochemistry was investigated for the cyclic products by NOE experiments. Gradient-selected one-dimensional NOE experiments were conducted at 600 MHz for the dihydropyrans **7a**,**b**,**e** and the lactone **10f**. For the dihydropyrans a NOE interaction of H2 with one of the protons H6 is indicative of a pseudoaxial

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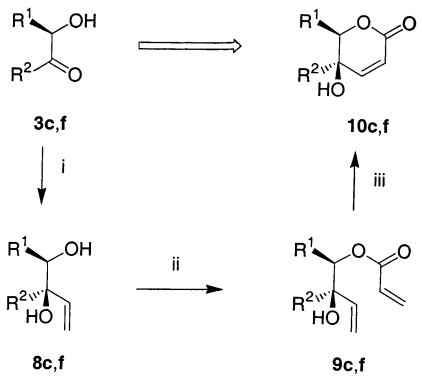
SCHEME 2[a]



[a] Reagents and conditions: (i) $H_2C{=}CHMgCl$, THF, −78 °C; (ii) $H_2C{=}CHCOCl$, NEt_3, DCM (10 mol % of DMAP for **9c**); (iii) B (4 mol %), toluene, 70 °C

TABLE 2. Synthesis of Arylated Lactones

3	R^1	R^2	% yield of **8** (dr)	**%** yield of **9**	**%** yield of **10**
(*R*)-**3c**	3-OCH_3-Ph	3-OCH_3-Ph	76 (17:1)	80	95
(*R*)-**3f**	$-CH_3$	3-Cl-Ph	81 (>19:1)	72	90

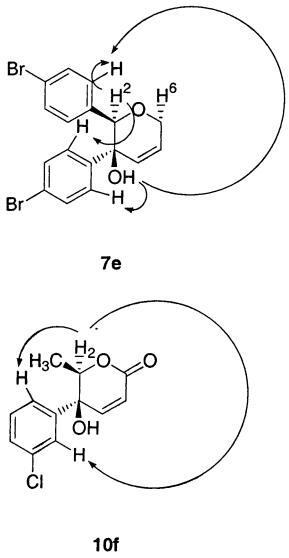


FIGURE 3. Representative NOE interactions in **7e** and **10f**.

orientation of these protons. H2 shows an NOE to the ortho-protons of the aromatic ring in the 3-position and to the substituent in the 2-position. However, no NOE interaction to the OH proton was observed. In contrast, the OH proton shows NOEs to both aromatic substituents and to the olefinic proton H4, but not to H2. From these observations we conclude that the substituents at C2 and C3 are *trans*-arranged. These NOE interactions are summarized for the example **7e** in Figure 3. For the lactone series, NOEs were recorded for **10f**. Indicative NOE interactions are found between H2 and both ortho protons of the aryl moiety. NOE interactions between the methyl group in the 2-position and these ortho protons are significantly weaker (Figure 3).

The relative *RS*-stereochemistry of the alcohols **6** and **8** and the high degree of diastereoselectivity originates from a chelation effect first proposed by Cram ("Cram's cyclic model").[24,25] The oxygen of the α-allyloxy substituent or the hydroxy group and the carbonyl oxygen form a five-membered chelate complex, which is preferentially attacked from the sterically less shielded side, as outlined for the formation of **6a** in Figure 4. The addition of organomagnesium compounds to α-hydroxy ketones and factors governing the stereoselectivity of the addition step have already been thoroughly investigated.[25,26]

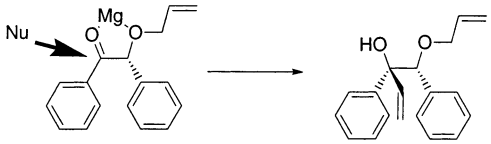


FIGURE 4. Rationalization of the stereochemical outcome in vinylation reactions.

In conclusion, we have developed a highly diastereoselective route to enantiomerically pure dihydropyrans and α,β-unsaturated lactones bearing one or two aromatic substituents. The synthetic concept is based on the use of α-hydroxy ketones which are conveniently obtained in enantiomerically pure form, a highly diastereoselective vinylation relying on efficient chelate control, and a ring-closing olefin metathesis step.

Experimental Section

General. All experiments were conducted in dry reaction vessels in an atmosphere of dry argon. Solvents were purified by standard procedures. ^1H NMR spectra were recorded at 400 or 500 MHz in $CDCl_3$ with $CHCl_3$ (δ 7.24 ppm) as internal standard. Coupling constants are given in hertz. ^{13}C NMR spectra were recorded at 100 or 125 MHz in $CDCl_3$ with $CDCl_3$ (δ 77.0 ppm) as internal standard. The number of coupled protons was analyzed by DEPT or APT experiments and is denoted in parentheses following the δ_C values. Signal assignment for cyclic products follows a numbering scheme where the oxygen atom is numbered as 1 and the α-carbon atom bearing the substituent R^1 (cf. Schemes 1 and 2) as C2. Selective 1D-NOE experiments were conducted using shaped pulses and pulsed field gradients at 600 MHz with a mixing time of 800 ms. IR spectra were recorded as films on NaCl or KBr plates or as KBr disks. The peak intensities are defined as strong (s), medium (m), and weak (w). Mass spectra were obtained at 70 eV. Optical purities were determined by HPLC using a HP-LC-1050 system equipped with a Daicel Chiralcel OD, a Daicel Chiralcel OD-H, or a Daicel Chiralpak AD column. Starting materials **3** were employed with ee values >99%, except for (*S*)-**3b** (ee 92%) and (*R*)-**3d** (ee 97%). The ruthenium catalyst **A**[27] was purchased from Fluka, the second generation catalyst **B** was prepared following a literature procedure.[28]

General Procedure for the Preparation of Allyloxy Ketones 4. To a solution of the corresponding α-hydroxy ketone **3** (2.0 mmol) and allyl bromide (0.26 mL, 3.0 mmol) in ether (30 mL) was added silver oxide (700 mg, 3.0 mmol). The mixture was heated to reflux for 2 h, and stirring was continued at ambient temperature in the dark for 2 days. All solids were removed by filtration through a small pad of Celite,

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the solvent was removed in vacuo, and the residue was purified by flash chromatography on silica using cyclohexane/MTBE mixtures as eluent.

(*R*)-2-Allyloxy-1,2-diphenylethanone (4a). Starting from (*R*)-benzoin (**3a**) (700 mg, 3.3 mmol), **4a** (750 mg, 90%) was obtained. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.75; H, 6.25. MS (EI): *m*/*z* 253 ($M^+ + 1$, 10), 105 (100). IR (film): 1694 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−7.90 (2H), 7.44−7.38 (3H), 7.33−7.18 (5H), 5.88 (dddd, 1H, J = 17.3, 10.3, 5.5, 5.5), 5.60 (s, 1H), 5.23 (dddd, 1H, J = 17.3, 1.5, 1.5, 1.5), 5.15 (dddd, 1H, J = 10.3, 1.5, 1.5, 1.5), 4.04 (dm, 2H, J = 5.5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3 (0), 136.2 (0), 135.0 (0), 134.0 (1), 133.2 (1), 129.1 (1), 128.8 (1), 128.4 (1), 128.4 (1), 127.5 (1), 118.1 (2), 83.9 (1), 70.5 (2). $[\alpha]^{22}_D$ +36.4 (*c* 1.0, CH_2Cl_2).

(*S*)- and (*R*)-2-Allyloxy-1-phenylpropan-1-one ((*S*)-4b and (*R*)-4b). Starting from either enantiomer of **3b** (490 mg, 3.3 mmol), the corresponding enantiomer of **4b** (approximately 290 mg, 47%) and benzoic acid allyl ester were obtained as an inseparable mixture, which was used for subsequent transformations. The yield of **4b** was estimated from the NMR spectrum of the mixture. NMR spectroscopic data for **4b** (obtained from the mixture): ^1H NMR (400 MHz, $CDCl_3$): δ 8.00−7.94 (2H), 7.45 (m, 1H), 7.39−7.31 (2H), 5.81 (dddd, 1H, J = 17.3, 10.5, 5.8, 5.5), 5.17 (dddd, 1H, J = 17.3, 1.5, 1.5, 1.5), 5.08 (dm, 1H, J = 10.3), 4.67 (q, 1H, J = 7.0), 4.00 (ddm, 1H, J = 12.5, 5.5), 3.85 (ddm, 1H, J = 12.5, 5.8), 1.41 (d, 3H, J = 7.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5 (0), 134.1 (0), 133.2 (1), 128.6 (1), 128.5 (1), 128.5 (1), 117.5 (2), 77.9 (1), 70.5 (2), 18.7 (3).

(*R*)-2-Allyloxy-1,2-bis(3-methoxyphenyl)ethanone (4c). Starting from **3c** (565 mg, 2.1 mmol), **4c** (640 mg, 99%) was obtained.

(*R*)-2-Allyloxy-1,2-bis(2-chlorophenyl)ethanone (4d). Starting from **3d** (420 mg, 1.5 mmol), **4d** (361 mg, 75%) was obtained after purification by column chromatography on silica.

(*R*)-2-Allyloxy-1,2-bis(4-bromophenyl)ethanone (4e). Starting from **3e** (580 mg, 1.5 mmol), **4e** (450 mg, 73%) was obtained after purification by column chromatography on silica.

General Procedure for the Preparation of Vinyl Carbinols 6. A solution of the corresponding ketone **4** (4.0 mmol) in ether (100 mL) was cooled to −78 °C. A solution of vinylmagnesium chloride in THF (1.7 M, 4.7 mL, 7.9 mmol) was added, and the mixture was stirred until the starting material was completely consumed, as indicated by TLC. The mixture was poured onto aqueous NH_4Cl solution, the organic layer was separated, and the aqueous layer was extracted with MTBE. The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography on silica.

(1*R*,2*S*)-1-Allyloxy-1,2-diphenylbut-3-en-2-ol (6a). Starting from **4a** (0.70 g, 2.8 mmol), **6a** (0.77 g, 99%) was obtained. The enantiomeric excess of **6a** was determined by HPLC analysis (Chiralpak AD, eluent: isohexane/2-propanol 95:5, flow 0.9 $mL min^{-1}$, 20 °C) to be >99% after comparison with racemic **6a** under identical conditions. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.30; H, 7.15. MS (EI): *m*/*z* 281 ($M^+ + 1$, <5), 147 (70), 105 (100). IR (film): 3463 (br m), 1449 (m), 925 (m), 700 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24−7.20 (2H), 7.17−7.07 (6H), 7.03−6.98 (2H), 6.50 (dd, 1H, J = 17.5, 10.8), 5.73 (dddd, 1H, J = 17.0, 10.8, 5.3, 5.0), 5.29 (dd, 1H, J = 17.3, 1.3), 5.19 (dd, 1H, J = 10.8, 1.3), 5.09 (ddm, 1H, J = 17.0, 1.5), 5.05 (ddm, 1H, J = 10.8, 1.5), 4.48 (s, 1H), 3.88 (dddd, 1H, J = 13.0, 5.0, 1.5, 1.5), 3.65 (ddm, 1H, J = 13.0, 5.3), 2.63 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7 (0), 141.5 (1), 136.6 (0), 134.3 (1), 128.7 (1), 127.8 (1), 127.5 (1), 127.5 (1), 126.8 (1), 126.2 (1), 117.0 (2), 114.4 (2), 86.8 (1), 78.5 (0), 70.0 (2). $[\alpha]^{25}_D$ −8.6 (*c* 1.00, CH_2Cl_2).

(3*S*,4*R*)- and (3*R*,4*S*)-4-Allyloxy-3-phenylpent-1-en-3-ol ((3*S*,4*R*)-6b and (3*R*,4*S*-6b)). Starting from (*R*)-**4b** (290 mg, 1.5 mmol of a mixture with allyl benzoate), (3*S*,4*R*)-**6b** (220 mg, 67%) was obtained. Analogously, from (*S*)-**4b** (270 mg, 1.4 mmol), (3*R*,4*S*)-**6b** (190 mg, 62%) was obtained. In both cases the products were contaminated with allylbenzoate from the preceding step. MS (EI): *m*/*z* 191 ($M^+ - C_2H_3$, 100), 105 (85). ^1H NMR (400 MHz, $CDCl_3$): δ 7.44−7.40 (2H), 7.33−7.28 (2H), 7.21 (m, 1H), 6.34 (dd, 1H, J = 17.3, 10.5), 5.86 (dddd, 1H, J = 17.3, 10.8, 5.8, 5.3), 5.35 (dd, 1H, J = 17.3, 1.5), 5.25 (dddd, 1H, J = 17.3, 1.5, 1.5, 1.5), 5.18 (dd, 1H, J = 10.5, 1.5), 5.14 (dddd, 1H, J = 10.8, 1.5, 1.5, 1.5), 4.09 (ddm, 1H, J = 12.8, 5.3), 3.94 (ddm, 1H, J = 12.8, 5.8), 3.77 (q, 1H, J = 6.0), 2.73 (br s, 1H), 0.92 (d, 3H, J = 6.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9 (1), 134.9 (1), 128.7 (0), 128.0 (1), 126.7 (1), 125.4 (1), 116.8 (2), 113.5 (2), 79.8 (1), 78.8 (0), 70.7 (2), 13.7 (3).

(1*R*,2*S*)-1-Allyloxy-1,2-bis(3-methoxyphenyl)but-3-en-2-ol (6c). Starting from **4c** (598 mg, 1.9 mmol), **6c** (513 mg, 79%) was obtained.

(1*R*,2*S*)-1-Allyloxy-1,2-bis(2-chlorophenyl)but-3-en-2-ol (6d). Starting from **4d** (135 mg, 0.4 mmol), **6d** (130 mg, 85%) was obtained.

(1*R*,2*S*)-1-Allyloxy-1,2-bis(4-bromophenyl)but-3-en-2-ol (6e). Starting from **4e** (207 mg, 0.5 mmol), **6e** (190 mg, 90%) was obtained.

General Procedure for the Preparation of Dihydropyrans 7. To a solution of the corresponding diene **6** (3.9 mmol) in DCM (50 mL) was added the catalyst **A** (97 mg, 3 mol %). The mixture was stirred until the starting material was completely converted, as indicated by TLC. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica.

(2*R*,3*S*)-2,3-Diphenyl-3,6-dihydro-2*H*-pyran-3-ol (7a). Starting from **6a** (0.55 g, 1.9 mmol), **7a** (0.44 g, 90%) was obtained. Signal assignments in the H NMR spectrum are supported by NOE experiments. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.75; H, 6.35. MS (EI): *m*/*z* 251 ($M^+ - 1$, <5), 146 (100). IR (disk, KBr): 3510 (s), 1495 (m), 1447 (m), 766 (s), 698 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21−7.16 (3H, Ph), 7.13−7.04 (5H, Ph), 6.78−6.74 (2H, Ph), 6.09 (ddd, 1H, J = 10.0, 3.5, 1.5, *H*5), 6.02 (ddd, 1H, J = 10.0, 1.5, 1.5, *H*4), 4.57 (s, 1H, *H*2), 4.48 (ddd, 1H, J = 17.1, 3.5, 1.5, *H*6), 4.38 (ddd, 1H, J = 17.1, 1.5, 1.5, *H*6), 2.33 (br s, 1H, −O*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0 (0), 136.2 (0), 132.2 (1), 128.3 (1), 127.8 (1), 127.6 (1), 127.5 (1), 127.5 (1), 127.2 (1), 126.1 (1), 85.3 (1), 71.9 (0), 66.8 (2). $[\alpha]_D^{24}$ 17.1 (*c* = 0.69, CH_2Cl_2).

(2*R*,3*S*)- and (2*S*,3*R*)-2-Methyl-3-phenyl-3,6-dihydro-2*H*-pyran-3-ol ((2*R*,3*S*)-7b and (2*S*,3*R*)-7b). Starting from (3*S*,4*R*)-**6b** (214 mg, 1.0 mmol), (2*R*,3*S*)-**7b** (160 mg, 86%) was obtained. Analogously, from (3*R*,4*S*)-**6b** (140 mg, 0.6 mmol), (2*S*,3*R*)-**7b** (97 mg, 80%) was obtained. Signal assignments in the H NMR spectrum are based on NOE experiments. Colorless crystals, mp 86 °C. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.56; H, 7.45. MS (EI): *m*/*z* 189 ($M^+ - 1$, <5), 173 (100), 146 (80). IR (disk, KBr): 3463 (s), 1447 (m), 1117 (s), 994 (m), 700 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (dd, 2H, J = 8.5, 1.5, Ph), 7.32 (dd, 2H, J = 8.5, 7.0, Ph), 7.23 (tt, 1H, J = 7.0, 1.5, Ph), 6.01 (ddd, 1H, J = 10.0, 2.5, 2.5, *H*4/*H*5), 5.93 (ddd, 1H, J = 10.0, 1.5, 1.5, *H*4/*H*5), 4.32 (dm, 1H, J = 17.1, *H*6), 4.26 (dm, 1H, J = 17.1, *H*6), 3.68 (q, 1H, J = 6.3, *H*2), 2.58 (br s, 1H, −O*H*), 1.04 (d, 3H, J = 6.3, −C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.5 (0), 132.4 (1), 128.1 (1), 128.0 (1), 127.0 (1), 125.7 (1), 79.5 (1), 71.2 (0), 66.2 (2), 13.8 (3). (2*R*,3*S*)-(**7b**): $[\alpha]_D^{27}$ −79.5 (*c* 1.50, CH_2Cl_2). (2*S*,3*R*)-(**7b**): $[\alpha]_D^{27}$ +81.0 (*c* 1.02, CH_2Cl_2).

(2*R*,3*S*)-2,3-Bis(3-methoxyphenyl)-3,6-dihydro-2*H*-pyran-3-ol (7c). Starting from **6c** (217 mg, 0.6 mmol), **7c** (180 mg, 90%) was obtained.

(2*R*,3*S*)-2,3-Bis(2-chlorophenyl)-3,6-dihydro-2*H*-pyran-3-ol (7d). Starting from **6d** (102 mg, 0.3 mmol), **7d** (70 mg,

75%) was obtained. A higher amount of ruthenium catalyst (25 mg, 10 mol %) was required in this case.

(2*R*,3*S*)-2,3-Bis(4-bromophenyl)-3,6-dihydro-2*H*-pyran-3-ol (7e). Starting from **6e** (171 mg, 0.4 mmol), **7e** (139 mg, 78%) was obtained.

General Procedure for the Preparation of Diols 8. To a solution of the corresponding ketone **3** (2.3 mmol) in dry THF (20 mL) was added a solution of vinylmagnesium chloride (1 M solution in THF, 5.0 mL, 5.0 mmol) at −78 °C. The mixture was stirred at this temperature until the starting material was fully consumed as indicated by TLC. Aqueous workup followed by flash chromatography on silica yielded the corresponding diol **8**.

(1*R*,2*S*)-1,2-Bis(3-methoxyphenyl)-but-3-ene-1,2-diol (8c). Starting from **3c** (270 mg, 1.0 mmol), **8c** (230 mg, 76%) was obtained. The enantiomeric excess of **8c** was determined by HPLC analysis (Daicel Chiralcel OD, eluent: heptane/2-propanol 90:10, flow 1.0 mL min^{-1}, 20 °C) to be >99% after comparison with racemic **8c** under identical conditions. MS (EI, 70 eV): *m*/*z* 283 (3%, $M^+ - OH$), 165 (100). IR (film): 3474 (s), 1601 (s), 1585 (s), 1489 (s), 733 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (dd, 1H, J = 8.0, 8.0), 7.08 (dd, 1H, J = 8.0, 8.0), 6.88 (d, 1H, J = 7.7), 6.81 (m, 1H, Ar), 6.75−6.71 (2H), 6.68 (d, 1H, J = 7.5), 6.58 (m, 1H), 6.51 (dd, 1H, J = 17.2, 10.7), 5.49 (dd, 1H, J = 17.2, 1.0), 5.34 (dd, 1H, J = 10.7, 1.0), 4.87 (d, 1H, J = 3.0), 3.68 (s, 3H), 3.63 (s, 3H), 2.51 (s, 1H), 2.48 (d, 1H, J = 3.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (0), 158.9 (0), 143.7 (0), 140.7 (1), 139.8 (0), 128.8 (1), 128.5 (1), 120.1 (1), 118.5 (1), 115.4 (2), 113.9 (1), 113.0 (1), 112.8 (1), 111.9 (1), 79.7 (1), 79.2 (0), 55.2 (3), 55.1 (3). $[\alpha]_D^{22}$ +18.7 (*c* 1.30, CH_2Cl_2).

(2*R*,3*S*)-3-(3-Chlorophenyl)pent-4-ene-2,3-diol (8f). Starting from **3f** (420 mg, 2.3 mmol), **8f** (396 mg, 81%) was obtained. Anal. Calcd for $C_{11}H_{13}O_2Cl$: C, 62.12; H, 6.16. Found: C, 62.00; H, 5.95. MS (EI, 70 eV): *m*/*z* 211 (5%, $M^+ - 1$), 167 (71), 139 (100). IR (film): 3442 (s), 1596 (s), 1572 (s), 786 (s), 697 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (s, 1H), 7.30−7.18 (3H), 6.26 (dd, 1H, J = 17.1, 10.5), 5.46 (dd, 1H, J = 17.1, 1.0), 5.31 (dd, 1H, J = 10.5, 1.0), 4.06 (q, 1H, J = 6.3), 2.67 (s, 1H), 1.97 (s, 1H), 0.94 (d, 3H, J = 6.3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5 (0), 141.7 (1), 134.4 (0), 129.5 (1), 127.2 (1), 125.7 (1), 123.5 (1), 115.2 (2), 78.5 (0), 72.5 (1), 16.1 (3). $[\alpha]_D^{21}$ −36.0 (*c* 0.60, CH_2Cl_2).

General Procedure for the Preparation of Acrylates 9. To a solution of the corresponding diol **8** (1.1 mmol) in dry DCM (15 mL) was added triethylamine (0.50 mL, 3.3 mmol). The mixture was cooled to 0 °C, and freshly distilled acryloyl chloride (0.13 mL, 1.6 mmol) was added, followed by DMAP (11 mg, 0.1 mmol). After 30 min the starting material was completely consumed and the mixture was extracted with water. The organic layer was dried, filtered, and evaporated. The residue was purified by flash chromatography on silica to give the corresponding acrylate **9**.

Acrylic Acid (1*R*,2*S*)-2-Hydroxy-1,2-bis(3-methoxyphenyl)but-3-enyl Ester (9c). Starting from **8c** (130 mg, 0.4 mmol), **9c** (113 mg, 80%) was obtained. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.20; H, 6.25. MS (EI, 70 eV): *m*/*z* 283 ($M^+ - H_2C{=}CHCO_2H$, 5%), 210 (91), 181 (100). IR (film): 3489 (s), 2958 (s), 1724 (s), 1601 (s), 768 (s), 735 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (dd, 1H, J = 8.0, 8.0), 7.09 (dd, 1H, J = 8.0, 8.0), 6.94 (d, 1H, J = 8.0), 6.88 (m, 1H), 6.76−6.69 (3H), 6.60 (s, 1H), 6.46 (dd, 1H, J = 17.2, 11.0), 6.42 (d, 1H, J = 17.5), 6.16 (dd, 1H, J = 17.5, 10.5), 6.12 (s, 1H), 5.85 (d, 1H, J = 10.5), 5.40 (d, 1H, J = 17.2), 5.26 (d, 1H, J = 11.0), 3.70 (s, 3H), 3.63 (s, 3H), 2.34 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8 (0), 159.4 (0), 158.8 (0), 143.4 (0), 140.4 (1), 136.8 (0), 131.5 (2), 128.9 (1), 128.6 (1), 128.1 (1), 120.5 (1), 118.5 (1), 115.0 (2), 113.9 (1), 113.6 (1), 113.0 (1), 111.8 (1), 80.0 (1), 78.5 (0), 55.2 (3), 55.0 (3). $[\alpha]_D^{21}$ +12.0 (*c* 0.40, CH_2Cl_2).

Acrylic Acid (1*R*,2*S*)-2-(3-Chlorophenyl)-2-hydroxy-1-methylbut-3-enyl Ester (9f). Starting from **8f** (240 mg, 1,1 mmol), **9f** (210 mg, 72%) was obtained. Anal. Calcd for $C_{14}H_{15}O_3Cl$: C, 63.04; H, 5.67. Found: C, 63.05; H, 5.45. MS (EI, 70 eV): *m*/*z* 194 (5%, $M^+ - H_2C{=}CHCO_2H$), 167 (40), 55 (100). IR (film) 3491 (s), 1713 (s), 1635 (m), 1617 (m), 808 (m), 786 (m), 697 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.34 (d, 1H, J = 7.7), 7.29 (d, 1H, J = 7.7), 7.25 (dd, 1H, J = 7.7, 7.7), 6.41 (d, 1H, J = 17.2), 6.22 (dd, 1H, J = 17.0, 10.7), 6.11 (dd, 1H, J = 17.2, 10.5), 5.86 (d, 1H, J = 10.5), 5.41 (q, 1H, J = 6.2), 5.36 (d, 1H, J = 17.2), 5.21 (d, 1H, J = 10.7), 2.40 (s, 1H), 1.08 (d, 3H, J = 6.2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3 (0), 144.0 (0), 141.3 (1), 134.4 (0), 131.3 (2), 129.6 (1), 128.2 (1), 127.4 (1), 125.8 (1), 123.6 (1), 114.6 (2), 78.1 (0), 74.9 (1), 14.0 (3). $[\alpha]_D^{21}$ −24.5 (*c* 0.40, CH_2Cl_2).

General Procedure for the Ring Closing Metathesis of Acrylates 9. To a solution of the corresponding acrylate **9** (0.6 mmol) in toluene (30 mL) was added ruthenium complex **B** (19 mg, 4 mol %). The solution was heated to 70 °C until the starting material was completely consumed (approximately 1 h). The solvent was evaporated and the residue was purified by flash chromatography on silica to give the corresponding lactone **10**.

(5*S*,6*R*)-5-Hydroxy-5,6-bis(3-methoxyphenyl)-5,6-dihydropyran-2-one (10c). Starting from **9c** (130 mg, 0.4 mmol), **10c** (115 mg, 95%) was obtained as colorless crystals, mp 120 °C. Signal assignments in the H NMR spectrum are based on H,H-COSY, and signal assignments in the C NMR spectrum are based on C−H-correlation spectroscopy. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.85; H, 5.30. MS (EI, 70 eV): *m*/*z* 326 (M^+, 1%), 190 (100). IR (film): 3376 (s), 1721 (s), 1604 (s), 797 (s), 779 (s) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.23 (dd, 1H, J = 8.0, 8.0, C3-Ar-*H*5′), 7.06 (dd, 1H, J = 8.0, 8.0, C2-Ar-*H*5′), 6.98 (d, 1H, J = 9.9, H4), 6.83 (dd, 1H, J = 8.4, 2.2, C3-Ar-*H*4′), 6.79 (dd, 1H, J = 8.1, 2.2, C2-Ar-*H*4′), 6.74 (d, 1H, J = 7.7, C3-Ar-*H*6′), 6.66 (s, 1H, C3-Ar-*H*2′), 6.52 (s, 1H, C2-Ar-*H*2′), 6.48 (d, 1H, J = 7.7, C2-Ar-*H*6′), 6.28 (d, 1H, J = 9.9, H5), 5.54 (s, 1H, H2), 3.67 (s, 3H, C3-Ar-OCH_3), 3.59 (s, 3H, C2-Ar-OCH_3), 2.94 (s, 1H, −OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.8 (0, C6), 159.6 (0, C3-Ar-*C*-OCH_3), 158.9 (0, C2-Ar-*C*-OCH_3), 149.4 (1, C4), 142.0 (0, C3-Ar-*C*1′), 134.0 (0, C2-Ar-*C*1′), 129.5 (1, C3-Ar-*C*5′), 128.6 (1, C2-Ar-*C*5′), 121.6 (1, C5), 120.3 (1, C2-Ar-*C*6′), 118.1 (1, C3-Ar-*C*6′), 115.0 (1, C2-Ar-*C*4′), 113.9 (1, C3-Ar-*C*4′), 113.1, (1, C2-Ar-*C*2′), 111.8 (1, C3-Ar-*C*3′), 86.9 (1, C2), 70.9 (0, C3), 55.3 (3, C3-Ar-OCH_3), 55.1 (3, C2-Ar-OCH_3). $[\alpha]_D^{23}$ −75.9 (*c* 0.22, CH_2Cl_2).

(5*S*,6*R*)-5-(3-Chlorophenyl)-5-hydroxy-6-methyl-5,6-dihydropyran-2-one (10f). Starting from **9f** (150 mg, 0.6 mmol), **10f** (121 mg, 90%) was obtained as a colorless solid, mp 156 °C. Signal assignments in the H NMR spectrum are based on H,H-COSY, and signal assignments in the C NMR spectrum are based on C−H-correlation spectroscopy. Anal. Calcd for $C_{12}H_{11}O_3Cl$: C, 60.39; H, 4.65. Found: C, 60.30; H, 4.35. MS (EI, 70 eV): *m*/*z* 194 ($M^+ - H_3CCHO$, 95%), 131 (100). IR (film): 3406 (s), 1719 (s), 1063 (s), 833 (m), 792 (m), 696 (m) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.47 (s, 1H, Ar), 7.36−7.25 (3H, Ar), 6.88 (d, 1H, J = 9.5, H4), 6.20 (d, 1H, J = 9.5, H5), 4.62 (q, 1H, J = 6.5, H2), 3.28 (s, 1H, OH), 1.25 (d, 3H, J = 6.5, −CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9 (0, C6), 149.4 (1, C4), 142.6 (0, *ipso*-C, Ar), 134.7 (0, C−Cl, Ar), 129.9 (1, Ar), 128.4 (1, Ar), 126.0 (1, Ar), 123.8 (1, Ar), 121.8 (1, C5), 82.1 (1, C2), 69.9 (0, C3), 13.4 (3, −*C*H_3). $[\alpha]_D^{21}$ −73.5 (*c* 0.31, CH_2Cl_2).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of **4c**−**e**, **6d,e**, **7c**−**e,** and **8c**; analytical data for compounds **4c**−**e**, **6c**−**e**, and **7c**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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