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Stereoselective Syntheses of Enantiomerically Pure 2,5-disubstituted Dihydropyrans Based on Olefin Metathesis

Bernd Schmidt* and Stefan Nave

Universität Potsdam, Institut für Chemie, Organische Chemie II, Karl-Liebknecht-Strasse 24-25, Haus 25, D-14476 Golm, Germany

berschmi@rz.uni-potsdam.de

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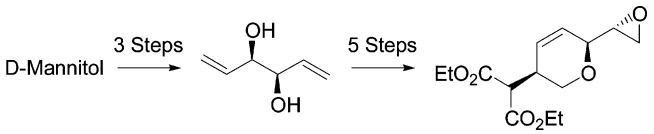

A short synthesis of 2,5-disubstituted dihydropyrans starting from D-mannitol as a chiral building block is described. Our synthetic approach combines ruthenium-catalyzed ring closing olefin metathesis and palladium-catalyzed nucleophilic substitution.

Introduction

2,5-Disubstituted tetrahydropyrans represent an important structural pattern in a number of natural products isolated from various sources and characterized by various biological activities. Important examples include the pseudomonic acids (e.g., PsA),[1] which show interesting antibiotic activity against a number of Gram-positive bacteria, as well as rhopaloic acids[2] and hippospongic acids,[3] which are both potent inhibitors of gastrulation in starfish embryos (Figure 1).[4]

With a view toward the synthesis of these natural products and some non-natural analogues, we started to investigate an olefin metathesis[5−9] based approach to this particular structural element (Scheme 1). We were interested in a general and flexible "platform"-type concept that would give access to several analogues from a minimum number of precursors. 2,5-Disubstituted dihydropyrans **2** should serve as common intermediates in such an approach because several methods for the functionalization of the C−C-double bond are available that should in principle give structurally diverse products **1**. A straightforward way to synthesize these dihydropyran intermediates would be the RCM of dienes **3**; however, this requires either the stereoselective synthesis of these metathesis precursors or a diastereoselective RCM[10−12] if R^2 in **3** is a vinyl group. The major problem with both options is that the stereocenters are located in a 1,4-distance, which makes it quite difficult to obtain high levels of stereoselectivity. This difficulty can be avoided

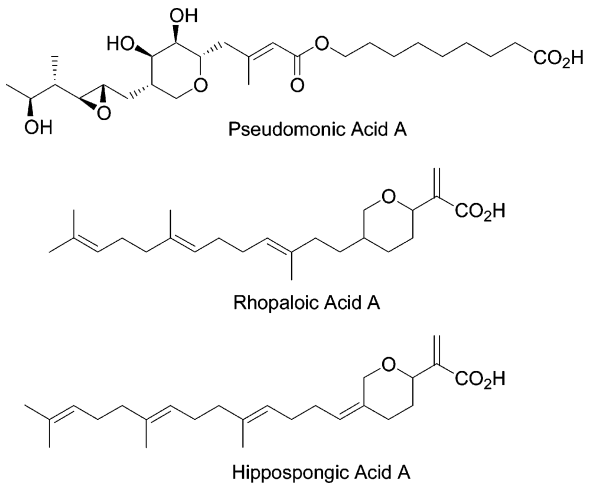

FIGURE 1. Prominent examples of natural products containing the 2,5-disubstituted tetrahydropyran core.

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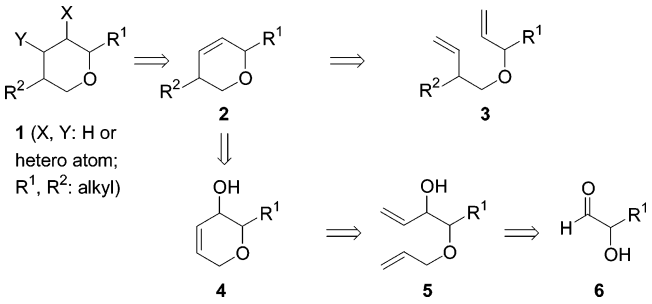
SCHEME 1. RCM-Based Approach to 2,5-Disubstituted Tetrahydropyrans



by starting from dihydropyrans **4** with a more easily accessible 1,2-arrangement of stereocenters. A stereospecific formal substitution, which proceeds with transposition of the C−C-double bond, should then give the required dihydropyrans **2** as single regio- and stereoisomers, or at least in high diastereomeric ratios. Methods available for the crucial transformation **4** → **2**, which have previously been applied to the synthesis of the tetrahydropyran core of pseudomonic acids and related structures,[1] are the esterenolate Claisen rearrangement[13−16] or a palladium-catalyzed allylic substitution.[17−24] The advantage of the former method is that in situ formation of the ester enolate by reaction of the free alcohol **4** with ortho esters or acetamide diacetals is possible; however, reaction temperatures are normally rather high. In contrast, the palladium-catalyzed allylic substitution proceeds at much lower temperatures, but requires conversion of the OH function into a leaving group prior to the substitution step. For the synthesis of 3-hydroxy-substituted dihydropyrans **4** we considered a two-step synthesis from α-hydroxy carbonyl compounds[25] **6**: first, a chelate controlled diastereoselective addition of a vinylmetal compound yields dienes **5**, which are then subjected to RCM (Scheme 1).[26,27]

In this paper, we report an evaluation of different strategies for the regio- and stereoselective synthesis of enantiomerically pure 2,5-disubstituted dihydropyrans, based on the combination of ruthenium-catalyzed olefin metathesis with either Claisen-rearrangement chemistry or palladium-catalyzed allylic substitution.

Results and Discussion

The starting point of our investigation was the 3-hydroxy-substituted dihydropyran **7**, which is available from methyl mandelate in three steps as outlined in Scheme 1.[26] In an initial experiment, **7** was treated with triethyl orthoacetate in refluxing xylene for 12 h to give a fair yield of the desired product **9**. Unfortunately, the reaction turned out to be rather sluggish and gave several unidentified and inseparable byproducts in small amounts. Conducting the reaction in a microwave oven reduced the reaction time to 20 min but did not improve the selectivity significantly. A parallel research project directed at the competition of RCM and an isomerization−Claisen rearrangement reaction[28−30] inspired an alternative approach to 2,5-disubstituted dihydropyrans: the original plan was to cyclize triene **11**, derived from **10**[27] by allylation, to dihydropyran **12**. Conversion of the metathesis catalyst to a selective isomerization catalyst in situ, using a protocol recently published by us,[31] should then give allyl vinyl ether **14** as an intermediate, which will subsequently undergo the Claisen rearrangement step to give **15**. However, RCM of triene **11** did not give the required dihydropyran **12** but a dihydrofuran **13** with high selectivity.[32,33] Therefore, the Tandem approach considered for this route could not be used and a two-step sequence was investigated: first, **7** was allylated to ether **12**, which was then treated with a combination of ethyl vinyl ether and the first-generation Grubbs' catalyst (**A**). Under these conditions, **A** is converted to a ruthenium hydride complex **B**, which is capable of mediating the isomerization of less hindered double bonds selectively.[30,31] Aldehyde **15** was obtained via this sequence in moderate yield as a 3:1 mixture of diastereomers. Products resulting from initial isomerization of the endocyclic double bond could not be detected, which makes it likely that the low yield must be attributed to subsequent decomposition of the aldehyde, rather than unselective double bond isomerization (Scheme 2).

With these rather unsatisfactory results in hand, we turned our attention to Pd-catalyzed allylic substitution chemistry, which had previously been applied to dihydropyrans derived from carbohydrates or furan-2-carbaldehyde by DeShong et al.[18] In the initial experiments, we wanted to examine two different Pd-catalyzed allylic substitution protocols for dihydropyran **7**. To this end, carbonate **17** was synthesized from **10** in 82% overall yield by treatment with 3-ethoxycarbonyl)benzotriazole-1-oxide ($BtOCO_2Et$),[34,35] followed by ring closing metathesis using 5 mol % of **A**. If RCM is the first step, the overall yield drops to 57%. Treatment of **17** with a cis-arrangement of substituents with the sodium salt of dimethyl malonate gives *cis*-**18a** as a single regio- and diastereoisomer, presumably via exo-attack of the π-allyl-Pd intermediate. With the soft nucleophile tributylvinyltin, an inseparable mixture of the two regioisomers **18b** and **18c** of the corresponding trans-product is obtained (Scheme 3). In both cases, structure elucidation was achieved by 2D-NMR experiments in combination with 1D-gradient-selected NOE experiments.

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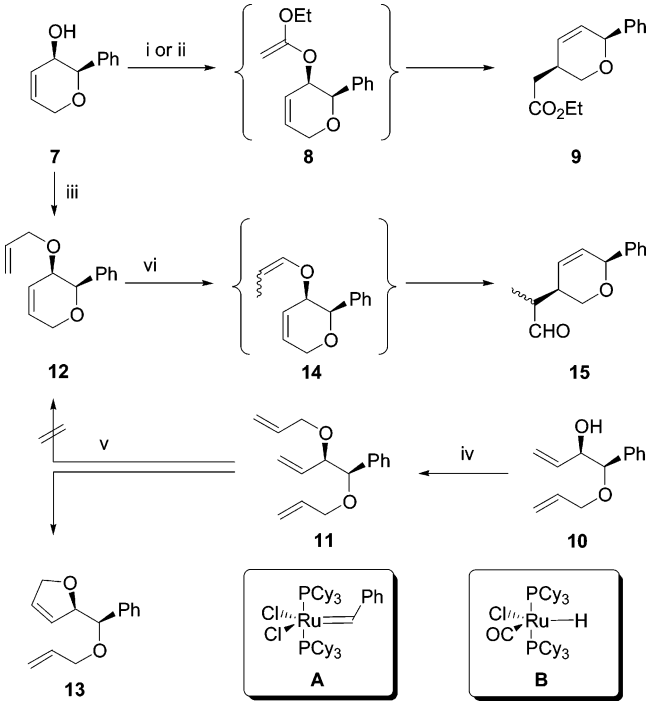
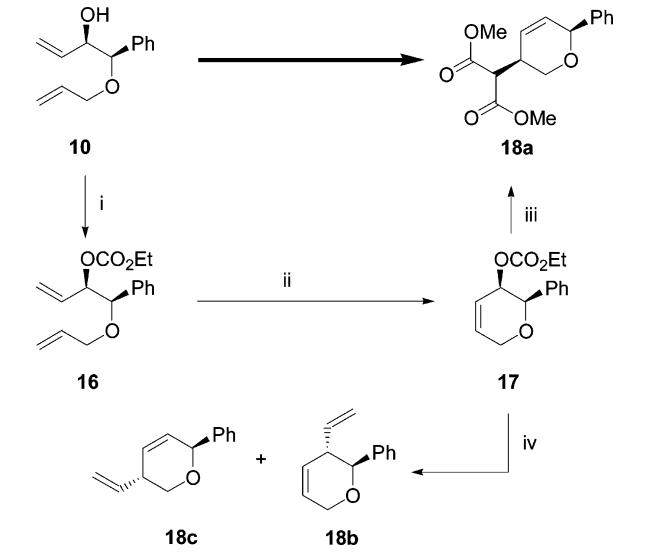
SCHEME 2. Application of Claisen Rearrangement Reactions to RCM-Derived Dihydropyrans[a]



[a] Reagents and conditions: (i) $H_3CC(OEt)_3$, H^+ (cat.), *m*-xylene, 135 °C, 12 h (58% of **9**); (ii) $H_3CC(OEt)_3$, H^+ (cat.), DMF, microwave irradiation, 160 °C, 20 min (53% of **9**); (iii) NaH, allyl bromide, THF, 0 °C (90% of **12**); (iv) NaH, allyl bromide, THF, 0 °C (89% of **11**); (v) **A** (5 mol %), DCM, 25 °C (54% of **13**); (vi) ethyl vinyl ether, **A** (5 mol %), toluene, 110 °C (35% of **15**, dr = 3:1).

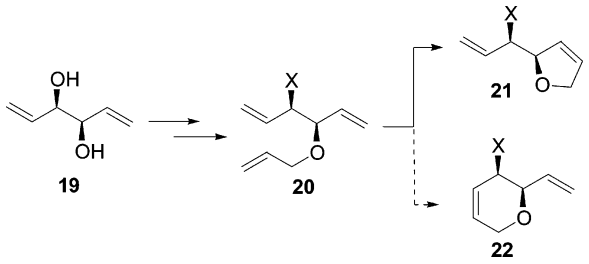
SCHEME 3. Pd-Catalyzed Allylic Substitution on Oxacyclic Scaffolds[a]



[a] Reagents and conditions: (i) $BtOCO_2Et$, NEt_3, pyridine, 20 °C (84%); (ii) **A** (3 mol %), DCM, 20 °C (98%); (iii) Na-malonate, $Pd(PPh_3)_4$ (2 mol %), PPh_3 (20 mol %) (80%); (iv) $H_2C{=}CHSnBu_3$, LiCl, $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), DMSO, 20 °C (52%, **18c**/**18b** = 3:1).

From the results discussed so far, it becomes obvious that both Claisen rearrangement and Pd-catalyzed allylic substitution are suitable methods for the conversion of metathesis-derived

SCHEME 4. Ring Size Selectivity Problem in RCM of Trienes Derived from 19



3-hydroxy-substituted dihydropyrans **4**. Nevertheless, two major drawbacks remain if the overall sequence outlined in Scheme 1 is considered: first, the number of α-hydroxy carbonyl compounds **6** available in enantiomerically pure form is rather limited, and only few of them have substituents R^1 which are easily modified to relevant C2-side chains. Second, stereocontrol of the addition of vinylmetal compounds to aldehydes **6** sometimes turns out to be quite difficult, with diastereomeric ratios of 5:1 in favor of the Cram-chelate product being typical. In searching for a solution to these problems, we came across the D-mannitol derived dienediol **19**.[36,37] As outlined in Scheme 4, one hydroxy group in **19** might be converted into a leaving group, while the other OH-group can be allylated to give a metathesis precursor **20**. RCM of **20** can result in either a five- (**21**) or a six-membered (**22**) ring. From the results discussed above for the RCM of **11** and previous experiences, it had to be expected that the dihydrofuran **21** would be strongly preferred in most cases (Scheme 4).[38]

A way to circumvent this problem is a selective functionalization of the C−C-double bond in **19** required for dihydrofuran formation *prior* to the metathesis step. To this end, one hydroxy group in **19** needs to be selectively protected, while the other OH-group can be used for a substrate directable reaction[39] of this C−C-double bond. Two different strategies have been applied for the selective mono-functionalization of dienediol **19**: (i) introduction of a protecting group which is sufficiently bulky to protect the second OH-group, such as TBDMS or trityl,[40,41] or (ii) in situ conversion to a dibutylstannyl acetal which then undergoes selective cleavage of one Sn−O-bond with benzyl bromide.[42,43] The latter method has mainly been used for the selective functionalization of carbohydrates.[44] Our global strategy toward 2,5-disubstituted dihydropyrans requires that one OH-group in **19** is allylated, while the other is converted into a leaving group. It would reduce the number of steps significantly, if the leaving group could simultaneously serve as a protecting group during the allylation step. We thought that this goal might best be achieved by cleaving the stannylene acetal **23** with an appropriate acid chloride.[45] However, while

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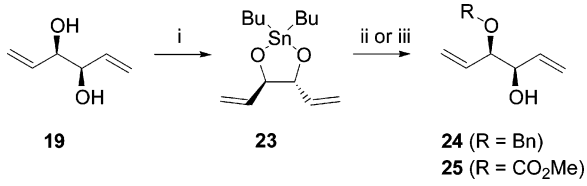
SCHEME 5. Desymmetrization of 19 via Cleavage of Its Stannylene Acetal[a]

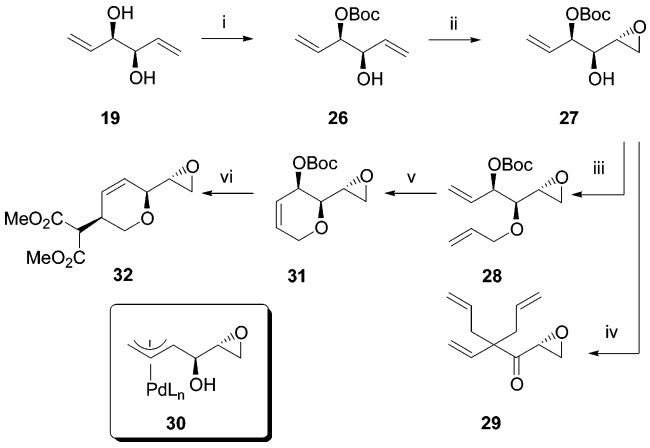


[a] Reagents and conditions: (i) Bu_2SnO, benzene, MS 4 Å; (ii) $PhCH_2Br$, $[Bu_4N]I$ (0.25 equiv), benzene, 80 °C (65%); (iii) $ClCO_2Me$, $[Bu_4N]I$ (0.25 equiv), benzene, 80 °C (no reaction).

cleavage of stannylene acetal **23** with benzyl bromide to give the monobenzyl ether **24** works well,[43,46] the analogous reaction with ethyl chloroformiate fails completely in our hands (Scheme 5).

Therefore, a method recently published by Clarke et al. that uses simple lanthanide-III salts as catalysts for selective monoacylation was applied to this problem.[47] With 10 equiv of acetic anhydride and $CeCl_3$ as a catalyst, a 2:1 ratio of mono- and bis-acylated products was obtained. For diethyl dicarbonate, mono- and bisacylated products were formed in a ratio close to 1:1. Although these products were easily separated by column chromatography, we further investigated the selective monoacylation of **19** and were pleased to find that with Boc-anhydride and 10 mol % of $CeCl_3$ only the mono-Boc-protected alcohol **26** results. To access the required dihydropyran selectively, the next step was crucial: the C−C-double bond closest to the unprotected alcohol had to be functionalized regio- and stereoselectively. We thought that a substrate directable epoxidation would be the most reliable method to achieve this goal. From previous experiences[46] with mono-TBS or monobenzyl-protected derivatives of **19** we expected that a substrate controlled epoxidation using $VO(acac)_2$ and *t*-BuOOH would give the required product **27** with good regioselectivity, but only with poor diastereoselectivity. To overcome this drawback, Sharpless conditions were investigated for selective epoxidation of **26**. Based on the mnemonic device used for the prediction of the outcome of Sharpless-epoxidation reactions, L-(+)-diethyl tartrate was required for the matched case. Indeed, alcohol **27** could be isolated as a single isomer in good yield. In the following step, an O-allylation of the unprotected alcohol was required. While formation of the corresponding sodium alkoxide and its allylation is not an option in this particular case, because cleavage of the epoxide or scrambling of the Boc-protecting group will most likely occur,[48] treatment with silver oxide and allyl bromide did not give any of the desired product. To solve this problem, we considered a Pd-catalyzed allylation. We have recently described that this method is very useful for the formation of allyl ethers of sensitive, base-labile substrates such as α-hydroxy carbonyl compounds.[46] At the beginning, it was by no means clear that this method would give useful results if applied to alcohol **27** because this compound itself is an allylic carbonate and might be attacked by the Pd catalyst to give a π-allyl-Pd complex, which would subsequently undergo other reactions. Indeed, the standard conditions that had been successfully applied to α-hydroxy carbonyl compounds (2 equiv

SCHEME 6. Regio- and Stereoselective Synthesis of 2,5-Disubstituted Dihydropyran 32[a]



[a] Reagents and conditions: (i) $(Boc)_2O$ (2 equiv), $CeCl_3$ (10 mol %) (78%); (ii) (+)-DET, $Ti(OPr^i)_4$, Bu^tOOH, DCM, −30 °C (79%); (iii) $H_2C{=}CHCH_2OC(O)OBu^i$ (5 equiv), $[Pd(PPh_3)_4]$ (2.5 mol %), THF, 65 °C (44%); (iv) $H_2C{=}CHCH_2OC(O)OEt$ (2 equiv), $[Pd(PPh_3)_4]$ (2.5 mol %), THF, 65 °C (26%); (v) $[RuCl_2(PCy_3)_2{=}CHPh]$ (5 mol %), DCM, 25 °C (88%); (vi) $Na(MeO_2CCHCO_2Me)$, $[Pd(PPh_3)_4]$ (2.5 mol %), THF, 65 °C (74%).

of allyl ethyl carbonate, 2.5 mol % of $[Pd(PPh_3)_4]$[49]) did not give the required allyl ether **28**, but a diallylated ketone **29**. We reason that substrate **27** successfully competes with the allylating agent in forming a π-allyl-Pd complex **30**, which might subsequently rearrange to a Pd-enolate, which will then undergo double allylation. Consequently, the problem might be solved by increasing the amount of allylating agent to five equivalents. Under these conditions characteristic signals of allyl ether **28** could be detected in the ^1H NMR spectrum of the crude reaction mixture; however, the ratio of **28** to **29** was still estimated to be lower than 1:5. It has previously been reported that significantly better results are sometimes obtained if isobutyl rather than ethyl allyl carbonate is used for transition metal-catalyzed allylation reactions.[50,51] Indeed, with 5 equiv of allyl isobutyl carbonate, the amount of **29** was significantly reduced to approximately one-third, under otherwise identical conditions. The steric requirements of an isobutyl moiety appear to be the optimum, as the corresponding *tert*-butyl derivative gave **28** and **29** in a 1:1 ratio. RCM of **28** proceeds smoothly, giving the dihydropyran **31** in good yield. The required 2,5-disubstitution pattern was finally established via regio- and stereoselective attack of sodium dimethyl malonate to the π-allyl-Pd complex derived from dihydropyran **31**. Compound **32** was formed in good yield and as a single isomer (Scheme 6).

In conclusion, we have demonstrated that ring-closing olefin metathesis in combination with either ester enolate Claisen rearrangement or Pd-catalyzed allylic substitution gives access to 2,5-disubstituted dihydropyrans. A major advantage of Pd-catalyzed allylic substitutions as second C−C-bond forming step are the comparatively mild reaction conditions. As a consequence, sensitive functional groups such as the epoxide moiety in our case are tolerated throughout the entire sequence of steps. Application of the sequence outlined herein to relevant target molecules is currently in progress in our laboratory.

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Experimental Section

3-Allyloxy-2-phenyl-3,6-dihydro-2*H*-pyran (9). Compound **7** (176 mg, 1.0 mmol) was dissolved in *m*-xylene (10 mL). Triethyl orthoacetate (324 mg, 2.0 mmol) followed by propionic acid (15 mg (0.2 mmol) were added and the mixture heated to reflux for 20 h. After cooling, the solvent was evaporated in vacuo, and the remaining dark yellow oil was subjected to flash chromatography (silica, cyclohexane/MTBE 20:1), yielding **9** (144 mg, 58%) as a yellow oil. Alternatively, **7** (138 mg, 0.8 mmol) was dissolved in DMF (1 mL), and triethyl orthoacetate (1.11 g, 6.9 mmol) and propionic acid (10 mg, 0.1 mmol) were added. In a sealed quartz tube, the solvent was heated to 160 °C for 20 min by means of a Monomode MLS Ethos 1600 microwave oven. The workup was done as stated above, yielding **9** (102 mg, 53%) as a yellow oil. Due to the formation of numerous byproducts, it was not possible to obtain analytically pure samples of **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.27 (5 H), 5.94 (1 H, dm, J = 10.0), 5.80 (1 H, ddd, J = 10.0, 1.5, 1.5), 5.10 (1 H, ddd, J = 2.3, 2.3, 2.3), 4.14 (2 H, qd, J = 7.2, 1.0), 3.90 (1 H, dd, J = 11.3, 3.3), 3.81 (1 H, dm, J = 11.3 Hz), 2.61 (1 H, m), 2.61 (1 H, dd, J = 18.6, 8.0 Hz), 2.50 (1 H, dd, J = 18.8, 9.3 Hz), 1.24 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3 (0), 140.7 (0), 130.3 (1), 128.5 (1), 128.0 (1), 127.9 (1), 127.3 (1), 76.6 (1), 67.2 (2), 60.5 (2), 37.6 (2), 31.1 (1), 14.2 (3).

Carbonic Acid Ethyl Ester 2-Phenyl-3,6-dihydro-2*H*-pyran-3-yl Ester (17). Compound **16** (3.02 g, 11.0 mmol) was dissolved in dichloromethane (45 mL), and Grubbs' catalyst **A** (270 mg, 3.0 mol %) was added. After the mixture was stirred for 20 h, the solvent was evaporated and the brown residue subjected to chromatography (silica, cyclohexane/MTBE 10:1). Compound **17** (2.67 g, 98%) was obtained as a light brown liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (2 H, dm, J = 7.3), 7.32 (2 H, ddm, J = 7.3, 7.3), 7.25 (1 H, tt, J = 7.3, 1.4), 6.18 (1 H, ddd, J = 10.2, 3.6, 1.6), 6.08 (1 H, dddd, J = 10.2, 5.3, 2.2, 2.2), 5.15 (1 H, ddd, J = 5.4, 2.1, 2.1), 4.72 (1 H, d, J = 2.1), 4.47 (1 H, ddd, J = 17.2, 3.5, 1.9), 4.32 (1 H, dm, J = 17.2), 3.97−3.85 (2 H), 1.07 (3 H, t, J = 7.2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5 (0), 137.5 (0), 133.0 (1), 128.0 (1), 127.6 (1), 126.5 (1), 122.2 (1), 77.8 (1), 69.4 (1), 66.2 (2), 63.8 (2), 14.0 (3); IR (film, NaCl plates) ν 2983 (m), 2940 (m), 2823 (m), 1740 (s), 1257 (s), 1096 (s); LRMS (FAB) m/z 271 (M^+ + Na, 10), 249.2 (M^+ + H, 14), 247 (M^+ − H, 23) 105 (40), 58 (30), 42 (15). Anal. Calcd for $C_{14}H_{16}O_4$ (248.27): C, 67.7; H 6.5. Found: C, 67.5; H, 6.7.

2-(6-Phenyl-3,6-dihydro-2*H*-pyran-3-yl)malonic Acid Dimethyl Ester (18a). In an oven-dried, argon-filled two-neck 25 mL flask, **17** (248 mg, 1.0 mmol) was dissolved in THF (5 mL), and triphenylphosphine (53 mg, 20 mol %) and $Pd(PPh_3)_4$ (23 mg, 2 mol %) were added. In a separate oven-dried, argon-filled Schlenk tube, dimethyl malonate (396 mg, 3.0 mmol) was dissolved in THF (5 mL), and sodium hydride (60% suspension in mineral oil, 120 mg, 3.0 mmol) was added slowly under cooling. The sodium dimethylmalonate solution was transferred to the reaction flask via Teflon cannula, and the mixture was heated to reflux for 2 h. After cooling, the mixture was passed through a short pad of silica. The solvent and other volatiles were evaporated and the residue was subjected to flash chromatography (silica, cyclohexane/MTBE 5:1 → 4:1). Compound **18a** (231 mg, 80%) was obtained as a light yellow liquid: ^{1}H NMR (C_6D_6, 200 MHz) δ 7.40−7.10 (5 H, Ar−H), 5.91 (1 H, dddd, J = 10.2, 5.0, 2.3, 1.3, −C*H*=CHCH(Ph)−), 5.66 (1 H, dm, J = 10.2, −CH=C*H*CH(Ph)−), 4.88 (1 H, ddd, J = 2.3, 2.3, 2.3, −C*H*(Ph)−), 4.08 (1 H, ddd, J = 11.8, 1.7, 1.4, −OC*H*^{cis}H−), 3.86 (1 H, d, J = 9.3, −C*H*$(CO_2Me)_2$), 3.72 (1 H, dd, J = 11.8, 3.5, −OC*H*^{trans}H−), 3.38 (3 H, s, $-OCH_3$), 3.34 (3 H, s, $-OCH_3$), 3.00 (1 H, m, −C*H*CH$(CO_2Me)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6 (0, C=O), 168.6 (0, C=O), 140.1 (0, *ipso*-C (Ph)), 132.2 (1, −*C*H=CHCH(Ph)−), 128.5 (1, Ph), 128.1 (1, Ph), 127.3 (1, Ph), 125.2 (1, −CH=*C*HCH(Ph)−), 77.2 (1, -*C*HPh), 66.2 (2, −O*C*HH−), 54.4 (1, −*C*H$(COOMe)_2$), 52.6 (3, $-OCH_3$), 52.5 (3, $-OCH_3$), 34.1 (1, −*C*HCH$(COOMe)_2$); IR (film, KBr plates) ν 2977 (m), 2869 (m), 1739 (s), 1126 (s); LRMS (FAB) m/z 291 (M^+ + H, 6).

2-Phenyl-3-vinyl-3,6-dihydro-2*H*-pyran (18b) and 6-Phenyl-3-vinyl-3,6-dihydro-2*H*-pyran (18c). Compound **17** (257 mg, 1.0 mmol) was dissolved in DMF (1.7 mL), and LiCl (132 mg, 3.1 mmol) and vinyl tributylstannane (342 mg, 1.1 mmol) were added. To this was added $Pd_2(dba)_3{\cdot}CHCl_3$ (53.6 mg, 5.0 mol %), and the mixture was stirred for 20 h, after which time TLC (cyclohexane/MTBE 5:1) indicated complete conversion. The mixture was partitioned between water (10 mL) and diethyl ether (10 mL), and the aqueous layer was extracted twice with diethyl ether (5 mL each). The combined organic layers were washed three times with water (5 mL each), then twice with KF (saturated solution in 10% NH_3 (aq), 5 mL each), then with brine (5 mL). After drying with magnesium sulfate and evaporation of the solvents, the residue was subjected to chromatography (silica, cyclohexane/MTBE 10:1) to give the title compounds as an inseparable mixture (**18b**/**18c** = 1:3, 90 mg, 52%). NMR data for minor isomer **18b** as obtained from the mixture: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.27 (5 H, Ar-H), 5.92−5.80 (2 H, −C*H*=CH−), 5.56 (1 H, ddd, J = 17.3, 10.4, 8.2, −C*H*=CH_2), 5.01 (1 H, d, J = 10.4, −CH=C*H*$_2$), 4.94 (1 H, d, J = 17.3, −CH=C*H*$_2$), 4.36−4.28 (2 H, −OC*H*H−), 4.15 (1 H, d, J = 9.1, −OC*H*Ph−), 3.14 (1 H, m, −C*H*CH=); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.6 (0, *ipso*-C (Ph)), 137.2 (1, −*C*H=CH_2), 128.2, 127.9, 127.8, 127.3, 126.4 (1, Ph, −*C*H=CH−), 116.9 (2, =*C*H$_2$), 81.4 (1, −O*C*H(Ph)−), 66.2 (2, −O*C*HH−), 45.7 (1, −*C*HCH=CH_2). NMR-data for major isomer **18c** as obtained from the mixture: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.27 (5 H, Ar−H), 5.92−5.80 (2 H, −C*H*=CH−), 5.73 (1 H, ddd, J = 17.3, 10.3, 8.2, −C*H*=CH_2), 5.18 (1 H, d, J = 17.3, −CH=C*H*$_2$), 5.13 (1 H, d, J = 10.3, −CH=C*H*$_2$), 5.10 (1 H, s, −OC*H*Ph−), 4.07 (1 H, dd, J = 11.0, 5.3, −OCHH−), 3.53 (1 H, dd, J = 11.0, 8.4, −OCHH−), 3.14 (1 H, m, −C*H*CH=); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.0 (0, *ipso*-C (Ph)), 137.4 (1, −*C*H=CH_2), 129.6, 128.5, 128.1, 127.8, 127.4, (1, Ph, −*C*H=CH−), 116.4 (2, =*C*H$_2$), 76.2 (1, −O*C*H(Ph)−), 68.3 (2, −O*C*HH−), 39.0 (1, −*C*HCH=CH_2).

Carbonic Acid *tert*-Butyl Ester 2-Hydroxy-1-vinylbut-3-enyl Ester (26). Dienediol **19** (228 mg, 2.0 mmol) was dissolved in dichloromethane (6 mL), and $CeCl_3{\cdot}7\ H_2O$ (75 mg, 10 mol %) was added, followed by di-*tert*-butyl dicarbonate (873 mg, 4.0 mmol). The resulting gray mixture was stirred for 20 h and then partitioned between diethyl ether (10 mL) and aq NaOH (5%, 10 mL). The combined organic phases were washed twice with 10^{-4} N HCl (5 mL each) and dried with magnesium sulfate, and the solvent was evaporated in vacuo. After column chromatography, **26** (334 mg, 78%) was obtained as a colorless liquid. None of the bis-carboxylated dienediol could be detected: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.84 (1 H, ddd, J = 17.2, 10.6, 5.6), 5.80 (1 H, ddd, J = 17.3, 10.5, 6.7), 5.36 (1 H, d, J = 17.3), 5.36 (1 H, d, J = 17.3), 5.29 (1 H, d, J = 10.7), 5.23 (1 H, d, J = 10.6), 4.94 (1 H, dd, J = 6.5, 6.5), 4.18 (1 H, m), 2.24 (1 H, s(br)), 1.46 (9 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.7 (0), 135.7 (1), 132.6 (1), 119.4 (2), 117.4 (2), 82.6 (0), 80.1 (1), 73.7 (1), 27.7 (3); $[\alpha]^{20}_D$ +33.3 (*c* 0.82, CH_2Cl_2); IR (film, KBr-plates) ν 3467 (s), 2982 (s), 1747 (s), 1370 (s), 1286 (m), 1162 (m), 929 (s), 858 (s), 793 (m); LRMS (FAB) m/z 215 (M^+ + H, 50), 159 (100), 59 (80); HRMS (FAB) calcd for $C_{11}H_{19}O_4$ (M^+ + H) 215.1284, found 215.1308. Anal. Calcd for $C_{11}H_{18}O_4$ (214.26): C, 61.7; H 8.5. Found: C, 61.3; H, 8.4.

Carbonic Acid *tert*-Butyl Ester 1-(Hydroxyoxiranylmethyl)-allyl Ester (27). An oven-dried Schlenk tube was charged under an argon atmosphere with dichloromethane (55 mL). Freshly distilled titanium isopropylate (3.57 mL, 12.0 mmol) was dissolved slowly, and the solution was cooled to −30 °C. (*R*,*R*)-(+)-DET (2.4 mL, 14.0 mmol) was added. After an aging period of 15 min, the allylic alcohol **26** (2.14 g, 10.0 mmol) was added. After another 15 min, *tert*-butyl hydroperoxide (2.85 M solution in toluene, 8.8

mL, 25.0 mmol) was added slowly. The Schlenk tube was sealed carefully and stored in a refrigerator at −30 °C for 19 d. After that time, TLC (silica, cyclohexane/MTBE 2:1) showed complete conversion and formation of a single new product (R_f = 0.21). At −30 °C, a solution of ferric sulfate (5.0 g) in an aqueous tartaric acid solution (15%, 47 mL) was added. The biphasic system was allowed to warm to room temperature, stirred for 30 min, and then passed through a short pad of Celite. The aqueous layer was extracted twice with dichloromethane (50 mL each), washed with brine (30 mL), and dried with magnesium sulfate, and the solvents were evaporated in vacuo. After column chromatography (silica, cyclohexane/MTBE 5:1 → 1:1), **27** (1.82 g, 79%) was obtained as a colorless liquid which is diastereomerically pure as shown by ^{1}H and ^{13}C NMR: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (1 H, ddd, J = 17.3, 10.6, 6.6), 5.40 (1 H, dm, J = 17.3), 5.32 (1 H, d, J = 10.6), 5.12 (1 H, ddm, J = 6.5, 5.4), 3.79 (1 H, ddd, J = 5.4, 4.2, 4.2), 3.05 (1 H, ddd, J = 4.2, 4.2, 2.7), 2.81 (1 H, dd, J = 5.0, 2.7), 2.73 (1 H, dd, J = 5.0, 4.1), 2.32 (1 H, d, J = 4.2, 1.45 (9 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.6 (0), 132.2 (1), 119.4 (2), 82.7 (0), 78.1 (1), 70.8 (1), 51.3 (1), 43.9 (2), 27.7 (3); $[\alpha]^{22}_D$ +35.2 (*c* 1.98, CH_2Cl_2); IR (film, KBr plates) ν 3521 (s), 2983 (s), 2934 (s), 1747 (s), 1480 (s), 1277 (s), 791 (m); LRMS (FAB) *m*/*z* 231 (M^+ + H, 35), 175 (100); HRMS (FAB) calcd for $C_{11}H_{19}O_5$ (M^+ + H) 231.1233, found 231.1260. Anal. Calcd for $C_{11}H_{18}O_5$ (230.26): C, 57.4; H 7.9. Found: C, 57.0; H, 8.1.

Carbonic Acid 1-(Allyloxyoxiranylmethyl)allyl Ester *tert*-Butyl Ester (28). Alcohol **27** (69 mg, 0.3 mmol) was dissolved in anhydrous THF (1.5 mL). In a separate Schlenk tube, ethyl allyl carbonate (196 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (5.1 mg, 2.0 mol %) were dissolved in THF (1.5 mL) and transferred to the alcohol solution via Teflon cannula. The mixture was heated to reflux for 2 h and then passsed through a short pad of silica. After evaporation of all volatiles, the residue was subjected to chromatography (silica, cyclohexane/MTBE 5:1), yielding **28** (39 mg, 44%) as a yellowish liquid. Byproduct **29** could not be completely separated from **28**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (1 H, ddd, J = 17.3, 10.6, 6.6), 5.84 (1 H, dddd, J = 17.1, 11.6, 5.6, 5.6), 5.38 (1 H, d, J = 17.2), 5.37 (1 H, d, J = 17.2), 5.28 (1 H, d, J = 10.6), 5.21 (1 H, d, J = 17.2), 5.20 (1 H, m), 5.12 (1 H, d, J = 10.5), 4.12 (1 H, dd, J = 12.8, 5.5), 4.02 (1 H, dd, J = 12.8, 5.8), 3.42 (1 H, dd, J = 4.9, 4.8), 3.02 (1 H, ddd, J = 7.0, 4.0, 2.7), 2.79−2.72 (2 H), 1.45 (9 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.8 (0), 134.5 (1), 132.5 (1), 118.7 (2), 117.2 (2), 82.3 (0), 78.1 (1), 77.5 (1), 72.6 (2), 50.5 (1), 44.7 (2), 27.7 (3); $[\alpha]^{21}_D$ +35.2 (*c* 1.56, CH_2Cl_2); IR (film, KBr plates) ν 3080 (w), 2982 (m), 2933 (m), 2872 (m), 1745 (s), 1642 (w), 1370 (m), 1276 (s), 1164 (m), 926 (m), 859 (m); LRMS (FAB) *m*/*z* 271 (M^+ + H, 30), 215 (100); HRMS (FAB) calcd for $C_{14}H_{23}O_5$ (M^+ + H) 271.1546, found 271.1554.

2-Allyl-1-oxiranyl-2-vinylpent-4-en-1-one (29). Obtained from **27** (115 mg, 0.5 mmol), ethyl allyl carbonate (130 mg, 1.0 mmol), and $Pd(PPh_3)_4$ (6.1 mg, 1 mol %) in THF (5 mL) following the protocol described above for the preparation of **28**: yield 25 mg (26%) of **29** as a colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (1 H, dd, J = 17.7, 10.8, −CH═), 5.69−5.56 (2 H, −CH═), 5.38 (1 H, d, J = 10.8, ═C*H*$_2$), 5.23 (1 H, d, J = 17.7, ═C*H*$_2$), 5.11−5.05 (4 H, ═C*H*$_2$), 3.75 (1 H, dd, J = 4.3, 2.4, −C*H*(O)CH$_2$), 2.86 (1 H, dd, J = 6.9, 4.3, −CH(O)C*H*$_2$), 2.76 (1 H, dd, J = 6.9, 2.4, −CH(O)C*H*$_2$), 2.55 (2 H, dd, J = 14.4, 7.9, −C*H*$_2$CH═), 2.48 (2 H, d, J = 14.4, 6.9, −C*H*$_2$CH═); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.5 (0), 138.2 (1), 132.6 (1), 132.6 (1), 119.0 (2), 118.9 (2), 118.0 (2), 57.0 (0), 49.6 (1), 48.0 (2), 37.5 (2), 37.3 (2); $[\alpha]^{21}_D$ +38.8 (*c* 1.45, CH_2Cl_2); IR (film, KBr plates) ν 3078 (m), 2980 (m), 2917 (m), 2360 (w), 1717 (s), 1640 (m), 1444 (m), 1383 (m), 1253 (m), 1166 (w), 1079 (w), 995 (m), 921 (s), 872 (m); LRMS (FAB) *m*/*z* 215 (M^+ + Na, 90), 193 (M^+ + H, 20), 154 (60). HRMS (FAB) calcd for $C_{12}H_{17}O_2$ (M^+ + H) 193.1229, found 193.1256.

Carbonic Acid *tert*-Butyl Ester 2-Oxiranyl-3,6-dihydro-2*H*-pyran-3-yl Ester (31). Obtained from **28** (39 mg, 0.1 mmol) and Grubbs' catalyst **A** (5 mg, 5.0 mol %) in dichloromethane (1 mL), following the protocol described above for the preparation of **17**. After gradient chromatography (silica, cyclohexane/MTBE 5:1 → 2:1), **31** (31 mg, 88%) was obtained as a light brown liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.09−6.02 (2 H), 4.99 (1 H, m), 4.28 (1 H, ddm, J = 17.1, 2.5), 4.12 (1 H, d, J = 17.2), 3.54 (1 H, dd, J = 4.4, 2.1), 3.18 (1 H, m), 2.85 (1 H, dd, J = 5.3, 2.6), 2.79 (1 H, dd, J = 5.2, 4.2), 1.44 (9 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.2 (0), 132.8 (1), 121.8 (1), 82.4 (0), 75.0 (1), 66.9 (1), 65.6 (2), 50.3 (1), 45.0 (2), 27.7 (3); $[\alpha]^{22}_D$ +193.6 (*c* 0.83, CH_2Cl_2); IR (film, KBr plates) ν 2980 (m), 2934 (m), 1739 (s), 1479 (w), 1371 (m), 1278 (s), 1255 (s), 1160 (s), 1096 (m), 856 (m); LRMS (FAB) *m*/*z* 243 (M^+ + H, 25), 187 (70), 125 (40); HRMS (FAB) calcd for $C_{12}H_{19}O_5$ (M^+ + H) 243.1233, found 243.1212.

2-(6-Oxiranyl-3,6-dihydro-2*H*-pyran-3-yl)malonic Acid Dimethyl Ester (32). Obtained from **31** (121 mg, 0.5 mmol) according to the procedure described above for the praparation of **18**. After flash chromatography (silica, cyclohexane/MTBE 2:1), **32** (95 mg, 74%) was obtained as a colorless liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.91 (1 H, dd, J = 10.4, 4.8), 5.87 (1 H, d, J = 10.4), 3.86−3.84 (2 H), 3.73−3.71 (7 H), 3.56 (1 H, d, J = 9.8), 2.92 (1 H, m?), 2.80 (1 H, m), 2.78 (1 H, dd, J = 5.0, 4.00), 2.69 (1 H, dd, J = 5.0, 2.5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5 (0), 168.5 (0), 128.8 (1), 126.8 (1), 74.7 (1), 65.9 (2), 54.3 (1), 53.0 (1), 52.6 (3), 52.6 (3), 45.5 (2), 34.2 (1); $[\alpha]^{20}_D$ +17.6 (*c* 1.36, CH_2Cl_2); IR (film, KBr plates) ν 2956 (w), 2360 (w), 1733 (s), 1436 (m), 1259 (m), 1157 (m), 1085 (m), 1029 (w); LRMS (FAB) *m*/*z* 257 (M^+ + H, 100), 227 (30), 137 (50); HRMS (FAB) calcd for $C_{12}H_{17}O_6$ (M^+ + H) 257.1026, found 257.1042.

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Supporting Information Available: Experimental procedures for compounds **11**−**13**, **15**, and **16** and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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