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Note

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Bidirectional Synthesis of 6-Acetoxy-5-hexadecanolide, the Mosquito Oviposition Pheromone of *Culex quinquefasciatus*, from a C_2-symmetric Building Block using Olefin Metathesis Reactions

Bernd Schmidt,* Monib H. Petersen and Diana Braun

Universitaet Potsdam, Institut fuer Chemie, Karl-Liebknecht-Straße 24-25, D-14476 Potsdam-Golm, Germany.

e-mail: bernd.schmidt@uni-potsdam.de

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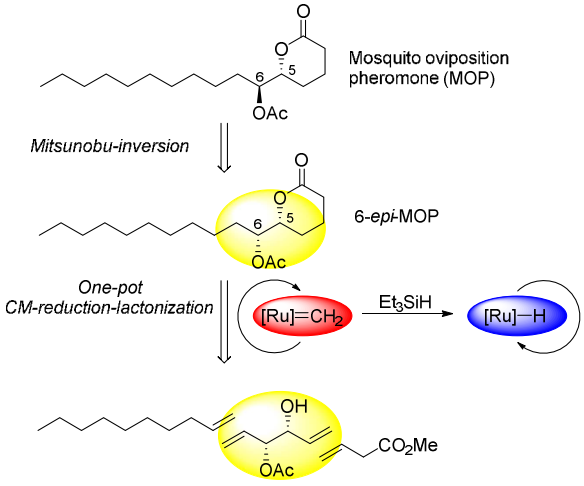


Abstract: (5*R*, 6*S*)-6-Acetoxy-5-hexadecanolide (MOP) is the oviposition pheromone of the mosquito *Cx. quinquefasciatus*, a vector of pathogens causing a variety of tropical diseases. We describe and evaluate herein three syntheses of MOP starting from mannitol-derived (3*R*, 4*R*)-hexa-1,5-diene-3,4-diol. This C_2-symmetric building block is elaborated through bidirectional olefin metathesis reactions into 6-*epi*-MOP, which was converted into MOP via Mitsunobu inversion. The shortest of the three routes makes use of two sequential cross metathesis reactions and an assisted tandem catalytic olefin reduction, induced by an in-situ conversion of a Ru-carbene to a Ru-hydride.

Culex quinquefasciatus is known as the southern house mosquito. The species is widely distributed in tropical and subtropical regions all over the world and has been known as a vector of many pathogens.[1-3] The outbreak of the Zika fever epidemic in Brazil in 2015 has raised concerns that not only mosquitoes of the genus *Aedes* (in particular *Ae. aegypti*) might be vectors of the Zika virus, but that transmission of the disease could also be possible through other even more common mosquitoes, such as *Cx. quinquefasciatus*.[4] Although recent laboratory experiments are inconclusive in this regard,[4-6] this question has stimulated a renewed interest in the chemical ecology of *Cx. quinquefasciatus* mosquitoes with a view to the development of sustainable vector control and monitoring programs based on the use of pheromone traps.[7,8] In the case of *Culex quinquefasciatus*, (5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**1**) has been identified as a pheromone that influences the site selection for oviposition.[9] Traps containing this compound or a mixture of all stereoisomers[10] can be used for collecting samples of gravid *Cx. quinquefasciatus* mosquitoes.[11-13] Shortly after the identification of **1** as the mosquito oviposition pheromone of *Cx. quinquefasciatus* in 1982[9] the first stereoselective synthesis of both enantiomers was reported.[14] This synthesis required multiple synthetic steps, several protecting group manipulations and chromatographic separations of diastereomers. Since then, numerous stereoselective syntheses of **1** or its stereoisomers have been reported, which reflect the rapid progress in synthetic methodology since the early 1980's.[15-32] The two most recent approaches to this target molecule use a chemoenzymatic[33] and an organocatalytic[29,34] epoxidation-lactonization sequence. The first example for an olefin metathesis based approach involves a sequence of cross metathesis (CM) of a fatty acid, epoxidation and lactonization and furnishes MOP (**1**) along with "other isomers".[35] Two syntheses using a ring closing metathesis (RCM) were published a few years later.[36,37] Another synthesis of MOP that uses olefin metathesis has been published by Quinn and coworkers. It relies on a dual RCM/CM functionalization[38,39] of (3*R*,4*S*)-4-

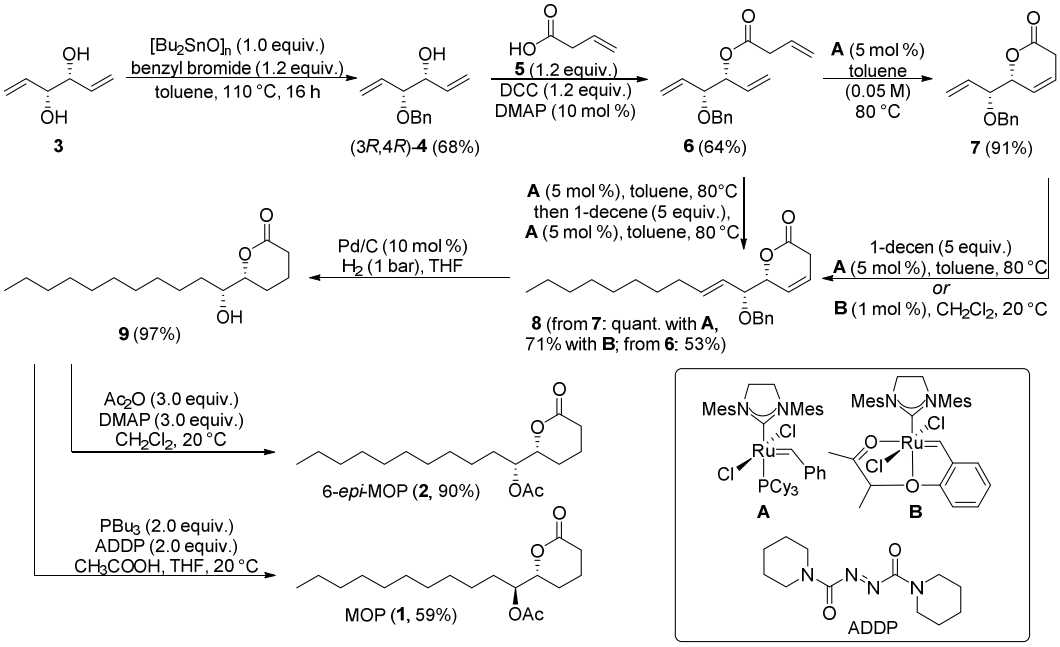
(benzyloxy)hexa-1,5-diene-3-ol ((3*R*,4*S*)-**4**), a chiral diene obtained through Sharpless epoxidation of divinyl carbinol, *O*-benzylation and epoxide opening with a sulfonium ylide.[40]

In this contribution we describe three syntheses of MOP (**1**) that have a bidirectional metathesis based elaboration of a hexa-1,5-diene-3,4-diol derivative with Quinn's approach in common, but start from the C_2-symmetric mannitol derived (3*R*,4*R*)-hexa-1,5-diene-3,4-diol (**3**).[41-48] One advantage of this and other C_2-symmetric building blocks is that a monofunctionalization results in identical products and that enantioselective transformations using chiral reagents or catalysts can be avoided. Not only **3**, but also its enantiomer, *ent*-**3**, is accessible from the chiral pool, which allows the transfer of a previously established strategy to the enantiomeric target structure without any modifications, if required.[43,49] Our synthetic routes make both MOP (**1**) and 6-*epi*-MOP (**2**) accessible in few steps with little or no protecting group efforts. A third variant proceeds from the monoacetate of **3** to 6-*epi*-MOP (**2**) as a one pot sequence of two CM steps, an assisted tandem catalytic hydrogenation[50,51] and an acid mediated lactonization.

At the outset we investigated an approach to 6-*epi*-MOP (**2**) starting from monobenzyl protected dienediol (3*R*,4*R*)-**4**,[48] an epimer of Quinn's starting material.[40] Steglich esterification[52] of (3*R*,4*R*)-**4** with vinyl acetic acid (**5**) furnished the metathesis precursor **6**, which underwent RCM to **7** in good yield and selectivity in the presence of second generation Grubbs' catalyst **A**.[53] Installation of the side chain through cross metathesis with 1-decene was accomplished from isolated and purified **7** using either second generation catalyst **A** or catalyst **B**,[54] which has emerged as a particularly useful catalyst for CM reactions.[43] With either catalyst the desired product **8** was obtained in similar yields between 70% and 75%, but **B** catalyzed the cross metathesis efficiently at ambient temperature and with a catalyst loading of just 1 mol%, whereas 5 mol% of catalyst and an elevated reaction temperature of 80 °C were required with catalyst **A**. The one-pot transformation of **6** into **8** via successive RCM and CM was investigated, but offered no synthetic advantage. Palladium on charcoal

catalyzed hydrogenation of both C-C-double bonds with concomitant debenzylation furnished **9**, which was acetylated to 6-*epi*-MOP (**2**) in high yield. For the synthesis of the mosquito oviposition pheromone **1** a Mitsunobu inversion[55] of the secondary alcohol **9** with acetic acid was envisaged. This step turned out to be surprisingly difficult and required optimization. With the most common phosphine, PPh_3, and either diisopropyl- (DIAD) or diethylazo dicarboxylate (DEAD) the reaction failed completely and unreacted starting material was recovered. Tsunoda et al. have reported that the combination of PBu_3 and the azodicarboxylate ADDP results in a more basic adduct than the standard combinations of DIAD or DEAD and PPh_3.[56] We thought that the somewhat lower acidity of acetic acid, compared with the commonly used *para*-nitrobenzoic acid, might be the reason for the complete failure and therefore tested the combination of ADDP and PBu_3, resulting in a synthetically useful yield of 59% of MOP (**1**). In the course of these investigations we noticed that water must be rigorously removed from the acetic acid, preferably by repeated distillation from P_4O_{10}, immediately before the reagent is used (**Scheme 1**).

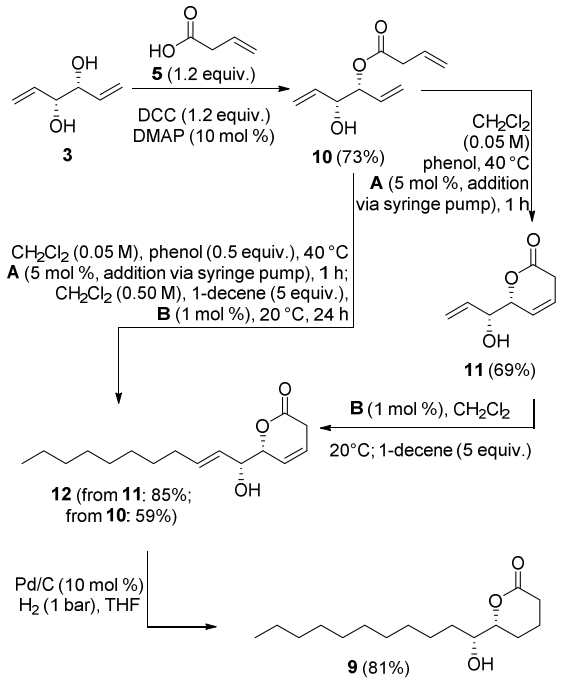
Scheme 1. Synthesis of MOP (**1**) and its 6-epimer **2** from protected dienediol (3*R*,4*R*)-**4**.



We then investigated a protecting group-free approach to the MOP- and 6-*epi*-MOP precursor **9** (**Scheme 2**). This synthesis started with a mono-acylation of the C_2-symmetric dienediol **3** to the mono-butenoate **10**, which underwent RCM to the dihydropyranone **11** with surprisingly low conversion under the RCM conditions previously established for the benzylprotected butenoate **6**. Literature reports on the effect of unprotected hydroxy groups on the rate and selectivity of metathesis reactions are inconsistent. In several cases a beneficial effect of allylic hydroxy groups was documented and explained by a hydrogen bonding between the proximal OH group and the Ru-chloro ligands.[57-59] On the other hand, attempted RCM of allyl alcohols was found to result in the formation of methyl ketones as byproducts and concommitant catalyst deactivation through formation of Ru-hydrides.[60] In any case, it appears to be unlikely that the low reactivity of **10** in the RCM step results from a catalyst inhibition by coordination of the hydroxy group to the Ru-centre. We did not detect any degradation products such as the above mentioned methyl ketones or isomerization products, which would point at a catalyst deactivation through Ru-hydride formation.[61] A possible explanation for the unsatisfactory rate of conversion under standard conditions might be that degenerate or non-productive[62-64] metathesis reactions become more favourable for allylic alcohol **10** compared to its benzyl protected analogue **6**. These non-productive metathesis events would slow down the RCM reaction and lead to competing catalyst deactivation. Standard optimization protocols using various amounts of catalysts **A** or **B**, different chlorinated or aromatic solvents and initial substrate concentrations varying from 0.01 to 0.10 mol•L^{-1} were unsuccessful and furnished **11** in yields not higher than 22%. Addition of phenol, which is a rate enhancing additive in metathesis reactions,[65] did not improve the yield. A breakthrough was eventually accomplished by addition of a catalyst solution to the RCM precursor via syringe pump in combination with phenol as a rate accelerating additive. We reason that the continuous addition of fresh precatalyst is beneficial for slow metathesis reactions, which are hampered by competing catalyst decomposition

processes.[66,67] In the next step, the cross metathesis of **11** and 1-decene was investigated. Under optimized conditions the CM product **12** was obtained in 85% yield by using five equivalents of 1-decene and just 1 mol % of catalyst **B**. We also investigated a one-pot RCM-CM sequence from **10** to **12** by combining the optimized conditions for RCM and CM steps. The yield for the one-pot RCM-CM sequence is virtually identical to the overall yield of the two step synthesis with isolation of **11**. Hydrogenation of **12** under atmospheric hydrogen pressure and with Pd/C as catalyst furnished **9** in 81% yield (**Scheme 2**).

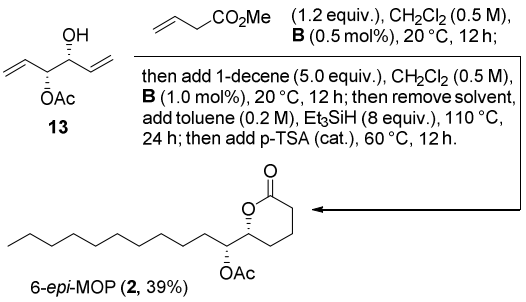
Scheme 2. Protecting group-free synthesis of MOP-precursor **9**.



Eventually, we investigated whether efficiency and protecting group economy of a metathesis based MOP-synthesis could even be further improved by exploiting Ru-catalyzed assisted tandem catalytic transformations.[50] In the olefin metathesis field,[51] such transformations can be used to functionalize a C-C-double bond formed in the metathesis step, without isolation of the intermediate and by using just one precatalyst.[68] These reactions rely on organometallic transformations of the metathesis catalyst in situ, which are triggered by suitable additives. The earliest examples combined olefin metathesis reactions and hydrogenations, which were

initiated by applying hydrogen pressure to completed metathesis reactions at elevated temperatures.[69,70] This induced a conversion of the Ru-carbene into a Ru-hydride species,[71,72] which subsequently catalyzes the hydrogenation. More recently, hydrogen surrogates were investigated both as chemical triggers for Ru-hydride formation and as hydrogenation reagents. Examples are 2-propanol,[73] formic acid[74] and triethylsilane.[61,75,76] We investigated an approach to 6-*epi*-MOP (**2**), starting from the monoacetate **13**,[58] that proceeds via two successive cross metathesis reactions and an assisted tandem catalytic hydrogenation using triethylsilane (**Scheme 3**).

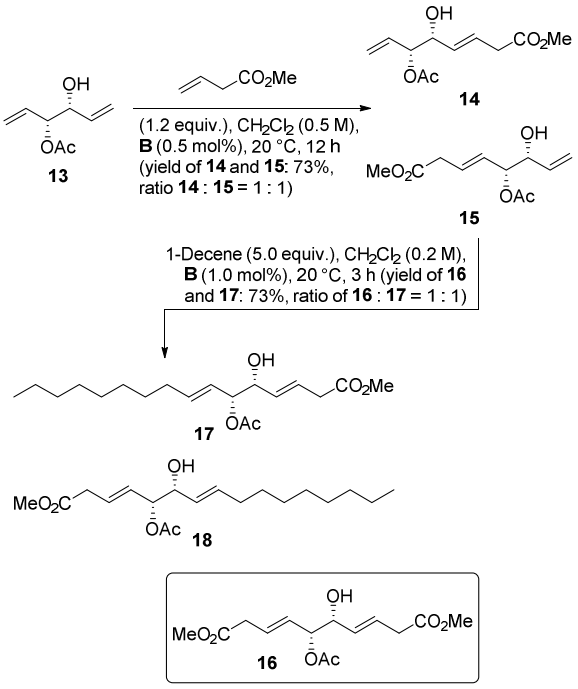
Scheme 3. Synthesis of 6-*epi*-MOP (**2**) through cross metathesis-hydrogenation.



First, the cross metathesis with methyl-3-butenoate was accomplished using only 0.5 mol% of precatalyst **B** at ambient temperature. Subsequently, 1-decene was added after evaporating excess methylbutenoate and redissolving the residue, together with a second (1.0 mol%) portion of **B**. The second cross metathesis also proceeded smoothly at ambient temperature. Exchanging the RCM solvent dichloromethane against toluene, followed by addition of triethylsilane and heating to reflux resulted in hydrogenation of both double bonds without addition of fresh catalyst. Acid catalyzed cyclization furnished the δ-lactone 6-*epi*-MOP (**2**) in 39% overall yield. Taking into account that six synthetic operations are performed in this sequence the yield is satisfactory. Nevertheless, we were interested in identifying the limiting factors. Our reasoning behind the design of this one-pot sequence was that the above mentioned OH-directing and activating effect[58,77] might be a useful selectivity control element

in this case. Thus, we expected that the double bond adjacent to the unprotected OH-group should be the preferred site for a cross metathesis reaction, and therefore used methyl-3-butenoate as the first CM partner. The second cross metathesis, with 1-decene at the position adjacent to the acetoxy group, was expected to proceed slower. To test these hypotheses, **13** and methyl-3-butenoate were subjected to various cross metathesis conditions (**Scheme 4**). Formation of the double cross metathesis product **16** was only observed with more than two equivalents of the CM partner. With 1.2 equivalents only monofunctionalized products were formed, but with virtually no regioselectivity: the isomers **14** and **15** were obtained as an inseparable mixture in a ratio of ca. 1 : 1. We subjected this mixture to the second cross metathesis step in the presence of a fivefold excess of 1-decene, to test whether methyl-3-butenoate is cleaved off under these conditions, but we observed only the expected cross metathesis products **17** and **18**, again as an inseparable mixture in a 1 : 1 ratio.

Scheme 4. Individual investigation of the two CM steps.



We conclude from these observations that the lack of selectivity of the first CM step is the main factor limiting the yield of the assisted tandem catalytic sequence, because only the hydrogenated product of intermediate **17** will readily undergo the final acid catalyzed cyclization to 6-epi-MOP. Neither double cross metathesis with the first CM partner nor undesired alkene redistribution in the second CM step lower the overall yield substantially. Preliminary experiments to overcome the insufficient regioselectivity of the first CM step involved testing of the presumably less reactive second generation Grubbs' catalyst **A** and its first generation counterpart under various conditions.[78] With both catalysts a higher catalyst loading of 5 mol% was required to obtain **14**/**15** in comparable yield, but the diminished reactivity of these catalysts did not result in an improved regioselectivity. Future investigations in our laboratory will address this issue further.

In summary, we describe and discuss three olefin metathesis based routes to the mosquito oviposition pheromone of *Cx. quinquefasciatus* starting from a C_2-symmetric mannitol derived dienediol. Two routes rely on combinations of RCM and CM steps. In the first route high yields can be achieved for the crucial olefin metathesis reactions under synthetically convenient routine conditions, but multiple steps, including protecting group operations, are required. The second route is protecting group free, but a very elaborate and time consuming protocol needs to be followed to overcome reactivity problems in the RCM step. The third route is the shortest and proceeds in one flask via two successive CM reactions and a tandem hydrogenation of both double bonds. Due to the high reactivity of the less common phosphine free catalyst **B** in CM reactions this route requires the lowest amount of metathesis catalysts, no additional noble metal catalyst for the hydrogenation step and is therefore in our opinion a showcase example for the application of assisted tandem catalytic transformations in target molecule synthesis.

Experimental Section

General methods. All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300 MHz, 500 MHz or 600 MHz in $CDCl_3$ or in C_6D_6 with C*H*Cl_3 (δ = 7.26 ppm) or C_6D_5H (δ = 7.16 ppm) as an internal standard. Coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz, 125 MHz or 151 MHz in $CDCl_3$ or in C_6D_6 with $CDCl_3$ (δ = 77.1 ppm) or C_6D_6 (δ = 128.1 ppm) as an internal standard. IR spectra were recorded as ATR-FTIR spectra. Wavenumbers (ν) are given in cm^{-1}. The peak intensities are defined as strong (s), medium (m) or weak (w). Low- and high resolution mass spectra were obtained by EI-TOF or ESI-TOF. Hexanes/MTBE mixtures of increasing polarity were used for column chromatography, starting with a hexanes : MTBE ratio of 10 : 1 (v/v), which was gradually reduced to 2 : 1 (v/v), if necessary.

(3*R*,4*R*)-4-(Benzyloxy)hexa-1,5-dien-3-yl but-3-enoate (6). To a solution of (3*R*,4*R*)-**4**[48] (1.230 g, 6.02 mmol) in CH_2Cl_2 (60 mL) was added vinyl acetic acid **5** (624 mg, 7.25 mmol), DMAP (75 mg, 0.60 mmol) and DCC (1.490 g, 7.20 mmol) at 0 °C. The mixture was warmed to ambient temperature and stirred until TLC showed full conversion (ca 12h). The precipitate was removed by filtration and the solution was washed with aq. HCl (1 M, 10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (three times 10 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica, using hexanes/MTBE mixtures as eluent, to furnish **6** (64%, 1.049 g, 3.85 mmol): colourless liquid; $[\alpha]_D^{26}$ +14.9 (*c* 0.135, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 5H), 6.06 – 5.67 (m, 3H), 5.48 – 5.42 (m, 1H), 5.40 – 5.15 (m, 6H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.44 (d, *J* = 12.2 Hz, 1H), 3.98 – 3.87 (m, 1H), 3.15 (dt, *J* = 6.9, 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 138.1, 134.1, 132.8, 130.2, 128.3, 127.6, 127.5, 119.7, 118.5, 118.2, 80.8, 75.5, 70.5, 39.2; IR (ATR) ν 1737 (s), 1248 (m); MS

(EI) *m*/*z* 196 (100), 273 (60, M^++H); HRMS (EI) calcd for $C_{17}H_{21}O_3$ [M^++H] 273.1491, found 273.1479.

(*R*)-6-((*R*)-1-(Benzyloxy)allyl)-3,6-dihydro-2*H*-pyran-2-one (7). To a solution of **6** (381 mg, 1.40 mmol) in toluene (30 mL) was added catalyst **A** (60 mg, 5.0 mol %) at 80 °C. The mixture was stirred at that temperature until TLC showed full conversion of the starting material (ca 2h). The solvent was evaporated and the residue was purified by column chromatography on silica, using petrol ether/MTBE mixtures as eluent, to furnish **7** (91%, 310 mg, 1.27 mmol): colourless liquid; $[\alpha]_D^{26}$ +97.9 (*c* 0.05, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 5.96 – 5.77 (m, 3H), 5.45 – 5.32 (m, 2H), 5.08 – 4.97 (m, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 3.99 (dd, *J* = 7.9, 3.9 Hz, 1H), 3.07 – 2.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 137.9, 133.7, 128.5, 127.8, 127.7, 123.2, 123.0, 121.2, 81.0, 80.7, 70.7, 30.4; IR (ATR) ν 1739 (s), 1375 (m); MS (EI) *m*/*z* 91 (100), 244 (12, M^+); HRMS (EI) calcd for $C_{15}H_{16}O_3$ [M^+] 244.1099, found 244.1092.

(*R*)-6-((*R*,*E*)-1-(Benzyloxy)undec-2-en-1-yl)-3,6-dihydro-2*H*-pyran-2-one (8). *Synthesis from dihydropyranone 7 with catalyst **B***: to a solution of **7** (360 mg, 1.47 mmol) in CH_2Cl_2 (3 mL) was added 1-decene (1030 mg, 7.35 mmol) and catalyst **B** (9.5 mg, 1.0 mol %) at ambient temperature. The reaction mixture was stirred until TLC showed full conversion of the starting material (ca 12h). All volatiles were evaporated and the residue was purified by column chromatography on silica using hexanes/MTBE mixtures as eluent to furnish **8** (88%, 462 mg, 1.29 mmol). *One-pot synthesis from triene **6** with catalyst **A***: to a solution of **6** (272 mg, 1.00 mmol) in toluene (20 mL) was added catalyst **A** (43 mg, 5.0 mol %) at 80 °C. The mixture was stirred at this temperature until TLC showed full conversion of the starting material (ca 2h). 1-Decene (701 mg, 5.00 mmol) and a second portion of catalyst **A** (43 mg, 5 mol %) were added and the reaction mixture was stirred at 80 °C for 12 hours. All volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica, using hexanes/MTBE mixtures as eluent, to furnish **8** (57%, 190

mg, 0.53 mmol): colourless liquid; $[\alpha]_D^{26}$ +37.6 (*c* 0.18, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 5.97 – 5.80 (m, 2H), 5.77 (dt, *J* = 15.5, 6.7 Hz, 1H), 5.46 (ddt, *J* = 15.5, 8.6, 1.5 Hz, 1H), 5.05 – 4.95 (m, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 3.94 (dd, *J* = 8.5, 3.9 Hz, 1H), 3.05 – 2.97 (m, 2H), 2.14 – 2.00 (m, 2H), 1.44 – 1.19 (m, 12H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 138.7, 138.2, 128.4, 127.7, 125.0, 123.3, 122.9, 81.0, 80.9, 70.2, 32.5, 31.9, 30.5, 29.5, 29.3, 29.2, 29.0, 22.7, 14.2; IR (ATR) ν 1744 (s), 1454 (m), 1375 (m); MS (ESI) *m*/*z* 357 (20, M^+); HRMS (EI) calcd for $C_{23}H_{33}O_3$ [M^+] 357.2430, found 357.2410.

(*R*)-6-((*R*)-1-Hydroxyundecyl)tetrahydro-2*H*-pyran-2-one (9). *Synthesis from benzyl protected diene **8***: To a solution of **8** (142 mg, 0.40 mmol) in THF (5 mL) was added Pd/C (10 wt-%, 0.8 mg) and the solution was saturated with hydrogen. The reaction mixture was kept under an atmosphere of hydrogen (1 bar) and stirred vigorously until TLC showed full conversion of the starting material (ca 36 h). All volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica using hexanes/MTBE mixtures as eluent to furnish **9** (97%, 105 mg, 0.39 mmol). *Synthesis from unprotected diene **12***: following the procedure given above for the debenzylation-hydrogenation of **8**, compound **12** (405 mg, 1.52 mmol) was hydrogenated using Pd/C (10 wt-%, 14 mg) as a catalyst to furnish **9** (81%, 332 mg, 1.23 mmol): colourless solid, mp 71 – 72 °C; $[\alpha]_D^{26}$ –8.0 (*c* 0.295, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (dt, *J* =10.8, 3.7 Hz, 1H), 3.59 - 3.48 (m, 1H), 2.72 – 2.33 (m, 3H), 1.96 – 1.66 (m, 4H), 1.53 – 1.48 (m, 2H), 1.23 (16H), 0.84 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 83.3, 73.3, 32.7, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.3, 25.5, 24.2, 22.7, 18.5, 14.1; IR (ATR) 3422 (m), 1750 (s), 1261 (m); MS (ESI) *m*/*z* 271 (100, M^++H); HRMS (ESI) calcd for $C_{16}H_{30}O_3Na$ $[M+Na]^+$ 293.2093, found 293.2096. All analytical data match those previously reported for **9**.[29]

(*R*)-1-((*R*)-6-Oxotetrahydro-2*H*-pyran-2-yl)undecyl acetate (6-*epi*-MOP, 2). To a solution of **9** (30 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was added acetic anhydride (34 mg, 0.33 mmol)

and DMAP (40 mg, 0.33 mmol). The reaction mixture was stirred at ambient temperature until TLC showed full conversion of the starting material (ca 4 h). It was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aq. solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2 (three times 5 mL). The combined organic layers were washed with water and brine and then dried with $MgSO_4$. All volatiles were evaporated under reduced pressure and the residue was purified by column chromatography on silica, using hexanes/ethyl acetate mixtures as eluent to afford **2** (90%, 31 mg, 0.10 mmol): colourless oil; $[\alpha]_D^{26}$ +12.1 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.96 (ddd, J = 8.2, 5.6, 3.6 Hz, 1H), 4.34 (dt, J = 11.5, 3.3 Hz, 1H), 2.59 (dddd, J = 17.7, 6.2, 4.4, 1.5 Hz, 1H), 2.44 (ddd, J = 17.8, 9.4, 7.2 Hz, 1H), 2.08 (s, 3H), 1.96 – 1.90 (m, 1H), 1.83 (m, 2H), 1.71 – 1.64 (m, 2H), 1.61 – 1.54 (m, 1H), 1.31 – 1.19 (m, 16H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 170.7, 79.8, 73.9, 31.9, 30.0, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 25.4, 24.2, 22.7, 21.0, 18.4, 14.2; IR (ATR) ν 1733 (s), 1227 (s); MS (ESI) *m*/*z* 196 (100), 313 (33, M^++H); HRMS (ESI) calcd for $C_{18}H_{33}O_4$ $[M+H]^+$ 313.2379, found 313.2386. All analytical data match those previously reported for **2**[29] and *ent*-**2**.[34]

(*S*)-1-((*R*)-6-Oxotetrahydro-2*H*-pyran-2-yl)undecyl acetate (MOP, 1). 1,1'-(Azodicarbonyl)dipiperidine (ADDP, 70 mg, 0.185 mmol) and PBu_3 (70 μL, 0.185 mmol) were dissolved in dry and degassed THF (1.0 mL) at 0 °C and stirred for 0.5 h at this temperature. A solution of **9** (25 mg, 0.093 mmol) in THF (0.5 mL), followed by acetic acid (dried by repeated distillation from P_2O_5 immediately before use, 20 mg, 0.560 mmol) were added and the reaction mixture was allowed to warm to ambient temperature. After 4 hours, the mixture was quenched by addition of a saturated aq. solution of $NaHCO_3$ and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (three times 5 mL) and the combined organic layers were dried with $MgSO_4$. All volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica, using hexanes/ethyl acetate mixtures as eluent, to furnish **1** (59%, 17 mg, 0.054 mmol): colourless

oil; $[\alpha]_D^{26}$ –32.9 (*c* 0.175, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (ddd, *J* = 7.9, 5.7, 3.6 Hz, 1H), 4.33 (dt, *J* = 11.5, 3.3 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.46 – 2.38 (m, 1H), 2.06 (s, 3H), 1.95 – 1.88 (m, 1H), 1.86 – 1.77 (m, 2H), 1.69 – 1.61 (m, 2H), 1.61 – 1.54 (m, 1H), 1.34 – 1.22 (m, 16H), 0.84 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.7, 79.8, 73.9, 31.9, 29.9, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 25.3, 24.1, 22.7, 21.0, 18.4, 14.1; IR (ATR) ν 1734 (s), 1227 (s); MS (ESI) *m*/*z* 196 (100), 313 (12, M^++H); HRMS (ESI) calcd for $C_{18}H_{33}O_4$ $[M+H]^+$ 313.2379, found 313.2371. All analytical data match those previously reported for **1**.[29,34]

(3*R*,4*R*)-4-Hydroxyhexa-1,5-dien-3-yl but-3-enoate (10). To a solution of **3** (230 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) was added vinyl acetic acid (**5**, 208 mg, 2.40 mmol), DMAP (25 mg, 0.20 mmol) and DCC (495 mg, 2.40 mmol) at 0 °C. The ice bath was removed and the mixture was stirred at ambient temperature until TLC showed full conversion (~12h). The resulting precipitate was filtered off and the solution was washed with aq. HCl (1 M). The organic layer was separated and the aqueous layer was extracted with dichloromethane (three times 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica, using hexanes/MTBE mixtures as eluent, to furnish **10** (73%, 265 mg, 1.46 mmol): yellowish liquid; $[\alpha]_D^{26}$ +38.8 (*c* 0.385, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 – 5.72 (3H), 5.32 – 5.09 (7H), 4.15 (dd, *J*= 5.7, 5.6 Hz, 1H), 3.08 (d, *J* = 6.9 Hz, 2H), 2.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 135.9, 132.6, 130.0, 119.2, 118.9, 117.4, 77.1, 73.7, 39.2; IR (ATR) ν 3451 (m), 1722 (s), 1250 (m); MS (ESI) *m*/*z* 98 (100), 183 (8, M^++H); HRMS (ESI) calcd for $C_{10}H_{15}O_3$ $[M^+$+H] 183.1021, found 183.1029.

(*R*)-6-((*R*)-1-Hydroxyallyl)-3,6-dihydro-2H-pyran-2-one (11). *Without pseudo-high dilution conditions*: butenoate **10** (91 mg, 0.50 mmol) was dissolved in CH_2Cl_2 (10 mL) and heated to 40 °C. Catalyst **A** (22 mg, 5 mol %) was added to the refluxing solution and the mixture was stirred at this temperature for three hours. After cooling to ambient temperature

all volatiles were removed in vacuo and the residue was purified by chromatography on silica, using hexanes/MTBE mixtures as eluent, to furnish **11** (22%, 17 mg, 0.11 mmol). *With pseudo-high-dilution conditions in the presence of phenol*: to a refluxing solution of **10** (91 mg, 0.50 mmol) and phenol (24 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added a solution of catalyst **A** via syringe pump (22 mg, 5 mol %, dissolved in 2.0 mL CH_2Cl_2 at 0.05 mL•min^{-1}). After completed addition the mixture was heated for 1 h at 40 °C. After cooling to ambient temperature, all volatiles were removed in vacuo and the residue was purified by column chromatography on silica, using hexanes/MTBE mixtures as eluent, to furnish **11** (69%, 52 mg, 0.35 mmol): brownish oil; $[\alpha]_D^{26}$ +78.3 (*c* 0.255, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6) δ 5.94 (ddd, *J* = 16.9, 10.5, 6.2 Hz, 1H), 5.56 (dm, *J* = 10.1, Hz, 1H), 5.43 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.37 (dtd, *J* = 10.1, 3.6, 1.6 Hz, 1H), 5.20 (dd, *J* = 10.5, 1.4 Hz, 1H), 4.69 - 4.66 (m, 1H), 4.16 (ddt, *J* = 6.0, 4.8, 1.2 Hz, 1H), 3.70 (s(br), 1H), 2.84 (ddt, *J* = 21.7, 3.1, 2.7 Hz, 1H), 2.67 (dtd, *J* = 21.7, 3.6, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 135.1, 123.5, 122.9, 119.1, 82.2, 74.9, 30.3; IR (ATR) ν 3417 (m), 1718 (s); MS (ESI) *m*/*z* 98 (100), 155 (1, M^++H); HRMS (ESI) calcd for $C_8H_{11}O_3$ [M^++H] 155.0708, found 155.0705.

(*R*)-6-((*R*,*E*)-1-Hydroxyundec-2-en-1-yl)-3,6-dihydro-2*H*-pyran-2-one (12). *Synthesis from dihydropyranone **11**:* compound **11** (78 mg, 0.50 mmol) and 1-decene (351 mg, 2.50 mmol) were dissolved in CH_2Cl_2 (1.0 mL) and precatalyst **B** (3.0 mg, 1.0 mol %) was added. The reaction mixture was stirred at ambient temperature until TLC showed full conversion of the starting material (ca 12h). All volatiles were evaporated in vacuo and the residue was purified by column chromatography on silica using hexanes/MTBE mixtures as eluent to furnish **12** (85%, 114 mg, 0.43 mmol). *One-pot synthesis from triene **10***: compound **10** (91 mg, 0.50 mmol) and phenol (24 mg, 0.25 mmol) were dissolved in CH_2Cl_2 (10 mL). The solution was heated to 40 °C and and a solution of precatalyst **A** (22 mg, 5 mol %) in CH_2Cl_2 (2.0 mL) was slowly added via syringe pump (0.05 mL•min^{-1}). After completed addition the mixture was heated at 40 °C for 1 h, cooled to ambient temperature and evaporated. The residue was

redissolved in CH_2Cl_2 (1.0 mL) and 1-decene (351 mg, 2.50 mmol) and precatalyst **B** (3.0 mg, 1.0 mol %) were added. The solution was stirred for 24 h at ambient temperature. All volatiles were removed in vacuo and the residue was purified by column chromatography on silica using hexanes/MTBE mixtures as eluent to furnish **12** (59%, 79 mg, 0.29 mmol): colourless liquid; $[\alpha]_D^{26}$ +60.1 (*c* 0.295, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (dddd, J = 10.2, 3.3, 3.3, 1.5 Hz, 1H), 5.90 (dddd, J = 10.2, 2.6, 1.5, 1.5 Hz, 1H), 5.84 (dt, J = 15.3, 6.9 Hz, 1H), 5.55 (ddt, J = 15.4, 7.5, 1.4 Hz, 1H), 4.91 – 4.87 (m, 1H), 4.21 (dd, J = 7.5, 5.0 Hz, 1H), 3.15 – 3.08 (m, 2H), 2.24 (s, 1H), 2.14 – 2.04 (m, 2H), 1.42 – 1.34 (m, 2H), 1.33 – 1.23 (m, 10H), 0.91 (t, J = 6.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 136.9, 126.6, 123.2, 123.2, 82.5, 75.0, 32.4, 31.9, 30.3, 29.5, 29.3, 29.2, 29.0, 22.7, 14.2; IR (ATR) ν 3423 (w), 1728 (s); HRMS (ESI) calcd for $C_{16}H_{27}O_3$ [M^++H] 267.1960, found 267.1992.

Synthesis of 6-*epi*-MOP (2) from 13 via double CM and tandem hydrogenation. Compound **13** (156 mg, 1.00 mmol) and methyl-3-butenoate (120 mg, 1.20 mmol) were dissolved in CH_2Cl_2 (2.0 mL). Precatalyst **B** (3.27 mg, 0.5 mol %) was added and the solution was stirred at ambient temperature for 12 h. After this a second portion of precatalyst **B** (6.54 mg, 1.0 mol %) and 1-decene (701 mg, 5.00 mmol) were added and the solution was stirred for 16 h at ambient temperature. The volatile compounds were removed *in vacuo* and the residue was redissolved in toluene (5.0 mL). Et_3SiH (928 mg, 8.00 mmol) was added and the solution was stirred at 110 °C for 24 h. The mixture was cooled to 60 °C and *p*-TSA (5 mg) was added. After stirring for 12h at 60 °C the solution was quenched by addition of a satd. aq. solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (three times 10 mL) and the combined organic layers were dried with $MgSO_4$. All volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica, using hexanes/ethyl acetate mixtures as eluent, to furnish **2** (39%, 122 mg 0.39 mmol).

Methyl (5*R*,6*R*,*E*)-6-acetoxy-5-hydroxyocta-3,7-dienoate (14) and methyl (5*R*,6*R*,*E*)-5-acetoxy-6-hydroxyocta-3,7-dienoate (15). Compound **13** (78 mg, 0.50 mmol) and methyl-3-

butenoate (60 mg, 0.60 mmol) were dissolved in CH_2Cl_2 (1.0 mL). Precatalyst **B** (3.27 mg, 1.0 mol%) was added and the solution was stirred at ambient temperature for 12 h. The volatiles were then evaporated *in vacuo* and the residue was purified by column chromatography on silica using hexanes/MTBE mixtures as eluent to furnish **14** and **15** (73%, 85 mg, 0.37 mmol) as an inseparable 1 : 1 mixture: brownish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 – 5.75 (m, 2H), 5.65 – 5.56 (m, 1H), 5.39 – 5.20 (m, 3H), 4.21 (m, 1H), 3.68 (s, 3H), 3.10 (dm, J = 7.2 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 172.7, 171.3, 171.3, 137.1, 133.8, 132.9, 129.7, 128.5, 126.6, 120.2, 118.3, 78.0, 77.3, 74.8, 74.2, 53.1, 53.6, 38.5, 38.5, 22.2, 22.2; IR (ATR) ν 3421 (w), 1732 (s); HRMS (ESI) calcd for $C_{11}H_{16}O_5Na$ [M^++Na] 251.0895, found 251.0900.

Dimethyl (3*E*,5*R*,6*R*,7*E*)-5-acetoxy-6-hydroxydeca-3,7-dienedioate (16). Compound **13** (78 mg, 0.50 mmol) and methyl-3-butenoate (250 mg, 2.50 mmol) were dissolved in CH_2Cl_2 (1.0 mL). Precatalyst **B** (3.27 mg, 1.0 mol%) was added and the solution was stirred at ambient temperature for 12 h. The volatiles were then evaporated *in vacuo* and the residue was purified by column chromatography on silica using hexanes/ethyl acetate mixtures as eluent to furnish **16** (60%, 90 mg, 0.30 mmol): brownish liquid; $[\alpha]_D^{26}$ +6.2 (*c* 0.260, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 – 5.80 (m, 2H), 5.64 – 5.51 (m, 2H), 5.22 (dd, J = 6.4, 6.1 Hz, 1H), 4.19 (dd, J = 5.7, 5.5 Hz, 1H), 3.66 (s, 6H), 3.08 (d, J = 6.9 Hz, 4H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 171.6, 170.2, 132.0, 128.7, 127.4, 125.4, 76.3, 73.1, 52.0, 51.9, 37.5, 21.1; IR (ATR) ν 3522 (w), 1730 (s), 1232 (s); HRMS (ESI) calcd for $C_{14}H_{20}O_7Na$ [M^++Na] 323.1107, found 323.1082.

Methyl (3*E*,5*R*,6*R*,7*E*)-6-acetoxy-5-hydroxyhexadeca-3,7-dienoate (17) and methyl (3*E*,5*R*,6*R*,7*E*)-5-acetoxy-6-hydroxyhexadeca-3,7-dienoate (18). A mixture of isomers **14** and **15** (114 mg, 0.50 mmol) and 1-decene (350 mg, 2.50 mmol) were dissolved in CH_2Cl_2 (2.5 mL). Precatalyst **B** (3.27 mg, 1.0 mol%) was added and the solution was stirred at ambient temperature for 3 h. All volatiles were evaporated *in vacuo* and the residue was

purified by column chromatography on silica using hexanes/ethyl acetate mixtures as eluent to furnish **16** and **17** (73%, 125 mg, 0.37 mmol) as an inseparable 1 : 1 mixture: brownish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 – 5.80 (m, 1H), 5.84 – 5.69 (m, 1H), 5.63 – 5.53 (m, 1H), 5.46 – 5.35 (m, 1H), 5.24 – 5.10 (m, 1H), 4.20 – 4.05 (m, 1H), 3.68 (s, 3H), 3.09 (d, J = 7.1 Hz, 2H), 2.09 (s, 3H, isomer 1), 2.08 (s, 3H, isomer 2), 2.07 – 1.98 (m, 2H), 1.68 (s, 1H), 1.30 – 1.21 (m, 14H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 172.5, 171.2, 171.2, 138.3, 135.9, 135.9, 133.0, 129.8, 129.8, 128.5, 128.5, 127.9, 127.9, 126.0, 125.1, 77.5, 77.5, 74.7, 73.8, 52.9, 52.9, 38.4, 38.4, 33.3, 33.2, 32.8, 32.8, 30.4, 30.3, 30.2, 30.1, 30.0, 23.6, 22.1, 15.0; IR (ATR) 3451 (w), 1720 (s); HRMS (ESI) calcd for $C_{19}H_{32}O_5Na$ [M^++Na] 363.2147, found 363.2120.

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Supporting Information Available statement

Copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Footnotes

(1) Arensburger, P.; Megy, K.; Waterhouse, R. M.; Abrudan, J.; Amedeo, P.; Antelo, B.; Bartholomay, L.; Bidwell, S.; Caler, E.; Camara, F.; Campbell, C. L.; Campbell, K. S.; Casola, C.; Castro, M. T.; Chandramouliswaran, I.; Chapman, S. B.; Christley, S.; Costas, J.; Eisenstadt, E.; Feschotte, C.; Fraser-Liggett, C.; Guigo, R.; Haas, B.; Hammond,

M.; Hansson, B. S.; Hemingway, J.; Hill, S. R.; Howarth, C.; Ignell, R.; Kennedy, R. C.; Kodira, C. D.; Lobo, N. F.; Mao, C.; Mayhew, G.; Michel, K.; Mori, A.; Liu, N.; Naveira, H.; Nene, V.; Nguyen, N.; Pearson, M. D.; Pritham, E. J.; Puiu, D.; Qi, Y.; Ranson, H.; Ribeiro, J. M. C.; Roberston, H. M.; Severson, D. W.; Shumway, M.; Stanke, M.; Strausberg, R. L.; Sun, C.; Sutton, G.; Tu, Z.; Tubio, J. M. C.; Unger, M. F.; Vanlandingham, D. L.; Vilella, A. J.; White, O.; White, J. R.; Wondji, C. S.; Wortman, J.; Zdobnov, E. M.; Birren, B.; Christensen, B. M.; Collins, F. H.; Cornel, A.; Dimopoulos, G.; Hannick, L. I.; Higgs, S.; Lanzaro, G. C.; Lawson, D.; Lee, N. H.; Muskavitch, M. A. T.; Raikhel, A. S.; Atkinson, P. W. *Science* **2010**, *330*, 86-88.

(2) Bartholomay, L. C.; Waterhouse, R. M.; Mayhew, G. F.; Campbell, C. L.; Michel, K.; Zou, Z.; Ramirez, J. L.; Das, S.; Alvarez, K.; Arensburger, P.; Bryant, B.; Chapman, S. B.; Dong, Y.; Erickson, S. M.; Karunaratne, S. H. P. P.; Kokoza, V.; Kodira, C. D.; Pignatelli, P.; Shin, S. W.; Vanlandingham, D. L.; Atkinson, P. W.; Birren, B.; Christophides, G. K.; Clem, R. J.; Hemingway, J.; Higgs, S.; Megy, K.; Ranson, H.; Zdobnov, E. M.; Raikhel, A. S.; Christensen, B. M.; Dimopoulos, G.; Muskavitch, M. A. T. *Science* **2010**, *330*, 88-90.

(3) Turell, M. J. *J. Am. Mosq. Control Assoc.* **2012**, *28*, 123-126.

(4) Franca, R. F. O.; Neves, M. H. L.; Ayres, C. F. J.; Melo-Neto, O. P.; Filho, S. P. B. *PLOS Negl. Trop. Dis.* **2016**, *10*, e0004760.

(5) Guo, X.-x.; Li, C.-x.; Deng, Y.-q.; Xing, D.; Liu, Q.-m.; Wu, Q.; Sun, A.-j.; Dong, Y.-d.; Cao, W.-c.; Qin, C.-f.; Zhao, T.-y. *Emerging Microbes Infect.* **2016**, *5*, e102.

(6) Fernandes, R. S.; Campos, S. S.; Ferreira-de-Brito, A.; Miranda, R. M. d.; Barbosa da Silva, K. A.; Castro, M. G. d.; Raphael, L. M. S.; Brasil, P.; Failloux, A.-B.; Bonaldo, M. C.; Lourenço-de-Oliveira, R. *PLOS Negl. Trop. Dis.* **2016**, *10*, e0004993.

(7) Mordue Luntz, A. J. *Biochem. Soc. Trans.* **2003**, *31*, 128-133.

(8) Pitts, R. J.; Mozūraitis, R.; Gauvin-Bialecki, A.; Lempérière, G. *Acta Tropica* **2014**, *132, Supplement*, S26-S34.

(9) Laurence, B. R.; Pickett, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 59-60.

(10) Dawson, G. W.; Mudd, A.; Pickett, J. A.; Pile, M. M.; Wadhams, L. J. *J. Chem. Ecol.* **1990**, *16*, 1779-1789.

(11) Laurence, B. R.; Mori, K.; Otsuka, T.; Pickett, J. A.; Wadhams, L. J. *J. Chem. Ecol.* **1985**, *11*, 643-648.

(12) Hwang, Y.-S.; Mulla, M. S.; Chaney, J. D.; Lin, G.-G.; Xu, H.-J. *J. Chem. Ecol.* **1987**, *13*, 245-252.

(13) Mboera, L. E. G.; Takken, W.; Mdira, K. Y.; Pickett, J. A. *J. Med. Entomol.* **2000**, *37*, 172-176.

(14) Fuganti, C.; Grasselli, P.; Servi, S. *J. Chem. Soc., Chem. Commun.* **1982**, 1285-1286.

(15) Mori, K.; Otsuka, T. *Tetrahedron* **1983**, *39*, 3267-3269.

(16) Guo-qiang, L.; Hai-jian, X.; Bi-chi, W.; Guong-zhong, G.; Wei-shan, Z. *Tetrahedron Lett.* **1985**, *26*, 1233-1236.

(17) Barua, N. C.; Schmidt, R. R. *Tetrahedron* **1986**, *42*, 4471-4474.

(18) Zhi-Min, W.; Xin-Hua, Q.; Wei-Shan, Z. *Tetrahedron* **1990**, *46*, 1191-1198.

(19) Bonini, C.; Checconi, M.; Righi, G.; Rossi, L. *Tetrahedron* **1995**, *51*, 4111-4116.

(20) Singh, S.; Guiry, P. J. *Eur. J. Org. Chem.* **2009**, 1896-1901.

(21) Moriyasu, M.; Kato, A.; Hashimoto, Y. *Chem. Lett.* **1984**, *13*, 1181-1184.

(22) Ko, K. Y.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 5353-5362.

(23) Henkel, B.; Kunath, A.; Schick, H. *Liebigs Ann.* **1995**, 921-923.

(24) Henkel, B.; Kunath, A.; Schick, H. *J. Prakt. Chem.* **1997**, *339*, 434-440.

(25) Lohray, B. B.; Venkateswarlu, S. *Tetrahedron: Asymmetry* **1997**, *8*, 633-638.

(26) Couladouros, E. A.; Mihou, A. P. *Tetrahedron Lett.* **1999**, *40*, 4861-4862.

(27) Olagbemiro, T. O.; Birkett, M. A.; Mordue; Pickett, J. A. *J. Agric. Food Chem.* **1999**, *47*, 3411-3415.

(28) Michaelakis, A.; Mihou, A. P.; Couladouros, E. A.; Zounos, A. K.; Koliopoulos, G. *J. Agric. Food Chem.* **2005**, *53*, 5225-5229.

(29) Dong, H.-B.; Yang, M.-Y.; Zhang, X.-T.; Wang, M.-A. *Tetrahedron: Asymmetry* **2014**, *25*, 610-616.

(30) Sun, B.; Peng, L.; Chen, X.; Li, Y.; Li, Y.; Yamasaki, K. *Tetrahedron: Asymmetry* **2005**, *16*, 1305-1307.

(31) Ikishima, H.; Sekiguchi, Y.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron* **2006**, *62*, 311-316.

(32) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308-9309.

(33) Hurem, D.; Dudding, T. *RSC Adv.* **2014**, *4*, 15552-15557.

(34) Hurem, D.; Dudding, T. *RSC Adv.* **2015**, *5*, 101732-101739.

(35) Pederson, R. L.; Grubbs, R. H. Metathesis syntheses of pheromones or their components. US Patent Appl. 2002/0022471 A1, Feb 21, 2002.

(36) Prasad, K. R.; Anbarasan, P. *Tetrahedron: Asymmetry* **2007**, *18*, 2479-2483.

(37) Park, Y.; Tae, J. *Synthesis* **2010**, *2010*, 3627-3630.

(38) Virolleaud, M.-A.; Bressy, C.; Piva, O. *Tetrahedron Lett.* **2003**, *44*, 8081-8084.

(39) Virolleaud, M.-A.; Piva, O. *Synlett* **2004**, 2087-2090.

(40) Quinn, K. J.; Curto, J. M.; McGrath, K. P.; Biddick, N. A. *Tetrahedron Lett.* **2009**, *50*, 7121-7123.

(41) Voight, E. A.; Rein, C.; Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489-8499.

(42) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143-4145.

(43) Schmidt, B.; Kunz, O.; Petersen, M. H. *J. Org. Chem.* **2012**, *77*, 10897-10906.

(44) Schmidt, B.; Kunz, O. *Beilstein J. Org. Chem.* **2013**, *9*, 2544-2555.

(45) Rama Rao, A. V.; Mysorekar, S. V.; Gurjar, M. K.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 2183-2186.

(46) Crombez-Robert, C.; Benazza, M.; Fréchou, C.; Demailly, G. *Carbohydr. Res.* **1997**, *303*, 359-365.

(47) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71-74.

(48) Schmidt, B.; Nave, S. *Adv. Synth. Catal.* **2007**, *349*, 215-230.

(49) Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513-5516.

(50) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365-2379.

(51) Schmidt, B.; Krehl, S. Domino- and tandem olefin metathesis reactions. In *Olefin Metathesis—Theory and Practice*; Grela, K., Ed.; Wiley: Hoboken, 2014, p 187-232.

(52) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522-524.

(53) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

(54) Arlt, D.; Bieniek, M.; Karch, R. Novel Metathesis Catalysts. Int. Patent Appl. PCT/EP2007/007972, Sept. 13, 2007.

(55) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127-164.

(56) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639-1642.

(57) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378-8379.

(58) Schmidt, B.; Staude, L. *J. Org. Chem.* **2009**, *74*, 9237-9240.

(59) Fuwa, H.; Kawakami, M.; Noto, K.; Muto, T.; Suga, Y.; Konoki, K.; Yotsu-Yamashita, M.; Sasaki, M. *Chem. Eur. J.* **2013**, *19*, 8100-8110.

(60) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123-1125.

(61) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672-7687.

(62) Meek, S. J.; Malcolmson, S. J.; Li, B.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16407-16409.

(63) Stewart, I. C.; Keitz, B. K.; Kuhn, K. M.; Thomas, R. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2010**, *132*, 8534-8535.

(64) Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 16277-16284.

(65) Forman, G. S.; McConnell, A. E.; Tooze, R. P.; van Rensburg, W. J.; Meyer, W. H.; Kirk, M. M.; Dwyer, C. L.; Serfontein, D. W. *Organometallics* **2005**, *24*, 4528-4542.

(66) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202-7207.

(67) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414-7415.

(68) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817-3858.

(69) Dias, E. L.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2758-2767.

(70) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312-11313.

(71) Beach, N. J.; Camm, K. D.; Fogg, D. E. *Organometallics* **2010**, *29*, 5450-5455.

(72) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865-1880.

(73) Schmidt, B.; Krehl, S.; Sotelo-Meza, V. *Synthesis* **2012**, *44*, 1603-1613.

(74) Kusy, R.; Grela, K. *Org. Lett.* **2016**, *18*, 6196-6199.

(75) Menozzi, C.; Dalko, P. I.; Cossy, J. *Synlett* **2005**, 2449-2452.

(76) Schmidt, B.; Kunz, O. *Eur. J. Org. Chem.* **2012**, 1008-1018.

(77) Xu, C.; Liu, Z.; Torker, S.; Shen, X.; Xu, D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 15640-15643.

(78) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.