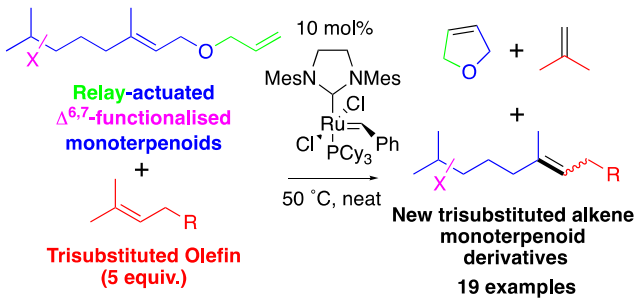
A Relay Strategy Actuates Pre-Existing Trisubstituted Olefins in Monoterpenoids to Form New Trisubstituted Olefins by Cross Metathesis

Karim A. Bahou,[a] D. Christopher Braddock,*[a] Adam G. Meyer,[b] G. Paul Savage,[b] Zhensheng Shi[a] and Tianyou He[a]

[a]*Department of Chemistry, Molecular Sciences Research Hub, White City Campus, 80 Wood Lane, London W12 0BZ, UK*

[b]*CSIRO Manufacturing, Jerry Price Laboratory, Research Way, Clayton, Victoria, 3168, Australia*



Abstract: A retrosynthetic disconnection-reconnection analysis of epoxypolyenes – substrates that can undergo cyclization to podocarpane-type tricycles – reveals relay-actuated $\Delta^{6,7}$-functionalized monoterpenoid alcohols for ruthenium benzylidene catalyzed olefin cross metathesis with homoprenyl benzenes. Successful implementation of this approach provided several epoxypolyenes as expected (*E*:*Z*, *ca.* 2-3:1). The method is further generalized for the cross metathesis of pre-existing trisubstituted olefins in other relay-actuated $\Delta^{6,7}$-functionalized monoterpenoid alcohols with various other trisubstituted alkenes to form new trisubstituted olefins. Epoxypolyene cyclization of an enantiomerically pure, but geometrically impure, epoxypolyene substrate provides an enantiomerically pure, *trans*-fused, podocarpane-type tricycle (from the *E*-geometrical isomer).

Introduction

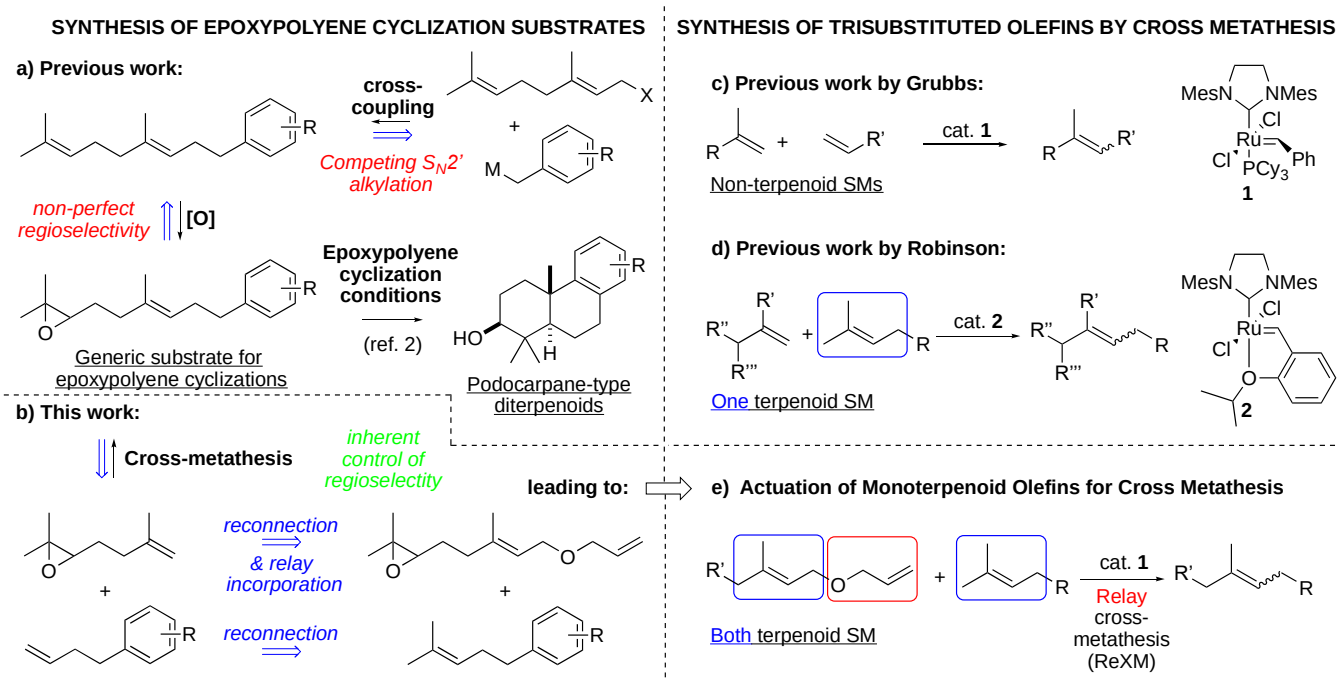


Figure 1. (a) Representative epoxypolyene cyclization and previous generic synthetic approach; (b) Proposed alternative disconnection, reconnections and relay incorporation; (c-d) Previous ruthenium benzylidene-catalyzed cross metathesis reactions to produce unfunctionalized trisubstituted olefins; (e) This work.

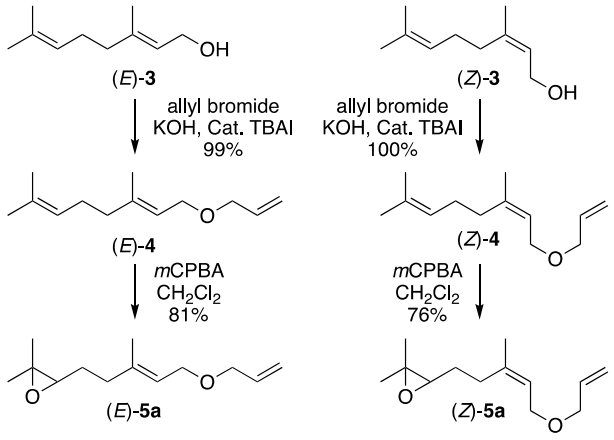
Biomimetically inspired polyene cyclizations have emerged as a powerful synthetic strategy for the stereocontrolled construction of complex polycarbocyclic scaffolds of biological significance,[1] where epoxypolyene cyclizations of terminally functionalized geranyl units with nucleophilic aromatic headgroups have provided synthetic access to podocarpane-type tricyclic diterpene skeleta (Figure 1a).[2] Such cyclization substrates are typically constructed in two steps via metal-catalyzed cross-coupling methodology of an electrophilic geranyl species in conjunction with a benzylic organometallic, and – either before or after C-C bond construction – regioselective functionalization of the geranyl alkene at the terminus of the chain (Figure 1a).[3] Each of these steps is subject to a potential disadvantage: the former is subject to competing allylic S_N2' substitution, and the latter to non-perfect regioselective oxidation, regardless of the order of implementation.[4] During the course of our studies, we had reason to consider an alternative disconnection of such functionalized linear monoterpenoid derivatives by olefin cross metathesis, but of the two terminal olefin species that are

revealed, the epoxide-containing component is synthetically non-simplified (Figure 1b). Nonetheless, a 'reconnection' operation[5] reveals a geraniol derivative with a pre-existing trisubstituted olefin that we expected could be actuated for cross metathesis by the application of Hoye's relay strategy.[6] For reasons outlined below, we also elected to 'reconnect' the terminal alkene component from the initial disconnection as a trisubstituted alkene.

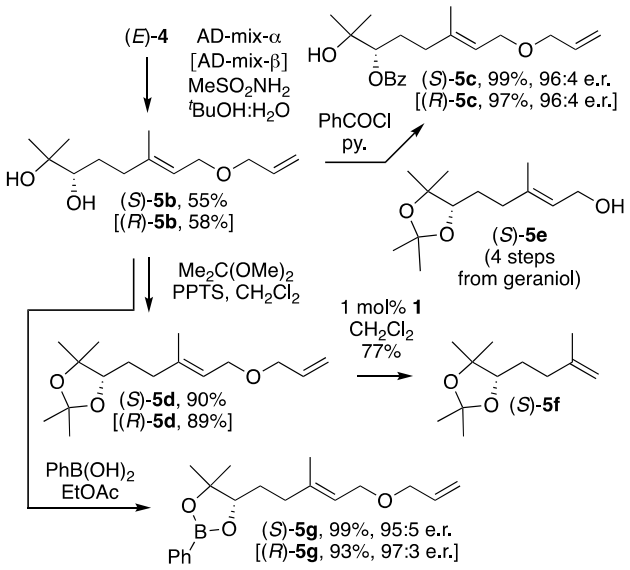
The catalyst(s) of choice for the above proposition would be the commercially available well-defined ruthenium benzylidenes as developed by Grubbs.[7] Such catalysts are widely used to accomplish the *ring-closing* metathesis of disubstituted, trisubstituted and even tetrasubstituted olefins.[8] In contrast, and quite surprisingly, there are only three reports on the formation of unfunctionalized trisubstituted olefins (as required here) by *cross* metathesis using ruthenium benzylidene pre-catalysts.[9] Grubbs and co-workers initially showed that ruthenium pre-catalyst **1** was competent for the cross metathesis of geminally disubstituted olefins with terminal olefins (Figure 1c).[10-11] Subsequently, Robinson and co-workers showed that the cross metathesis of sterically challenging allyl branched 1,1-disubstituted olefins performed considerably better using a (terpenoid) prenyl rather than an allyl partner using pre-catalyst **2** (Figure 1d).[12] With this latter literature precedent in mind, we therefore selected trisubstituted olefins as the cross metathesis partners (Figure 1b, reconnection).[13] As envisioned, this overall stratagem not only opens up the possibility of an alternative, modular, synthetic route to such cyclization precursors, but perhaps more significantly could provide a general approach to the functionalization of pre-existing trisubstituted olefins in acyclic monoterpenoid alcohols by cross metathesis (Figure 1e).[14] Herein, we report the success of this unprecedented olefin-olefin combination to form new unfunctionalized trisubstituted olefins by cross metathesis (Figure 1e), where the overall transformation can be classified as a relay cross metathesis. This relay *cross* metathesis reaction ("ReXM") distinguishes itself from the very limited literature precedent for such reactions by being the first such example to form isolated, unconjugated, trisubstituted alkenes where all previous reports have formed conjugated alkenes.[15,16]

Results and Discussion

Scheme 1. Synthesis of relay-modified $\Delta^{6,7}$-functionalized monoterpenes (*E*)-**5a** and (*Z*)-**5a**



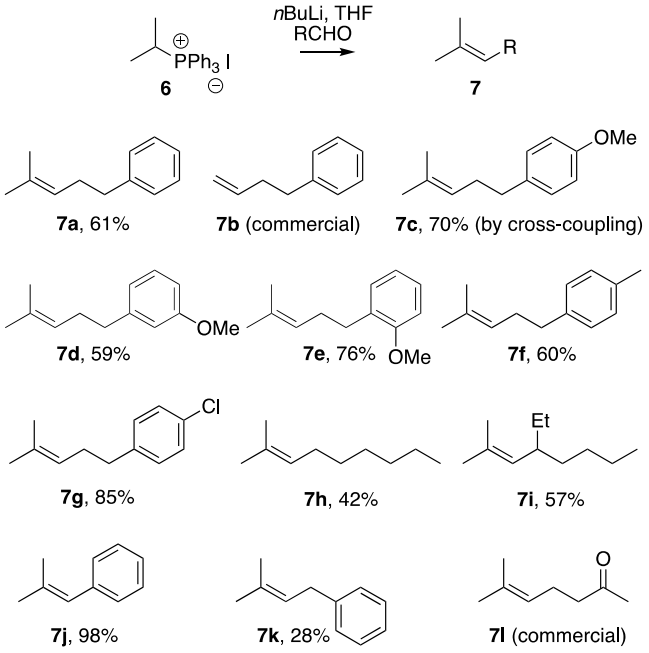
Scheme 2. Synthesis of various $\Delta^{6,7}$-functionalized monoterpenes **5b-g**.



We commenced our investigations with two main objectives in mind: i) demonstration of proof-of-principle ReXM of monoterpenoid alcohol derivatives with homoprenylbenzenes to prepare representative epoxypolyene cyclization substrates; ii) exemplification of the method as a general approach for the functionalization of pre-existing trisubstituted olefins in acyclic monoterpenoid alcohols. Accordingly, we assembled relay-modified $\Delta^{6,7}$-functionalized monoterpenes (*E*)-**5a** and (*Z*)-**5a** from geraniol [(*E*)-**3**] and nerol

[(*Z*)-**3**] via allylation[17] and epoxidation with *m*CPBA (Scheme 1). We also prepared diols (*S*)- and (*R*)-**5b** via Sharpless dihydroxylation[18] of triene (*E*)-**4** in excellent enantiomeric purity – confirmed by conversion to their respective benzoates **5c** and chiral stationary phase HPLC analysis (see SI) – and thence acetonides (*S*)- and (*R*)-**5d** (Scheme 2) by ketalization. Relay-free acetonide (*S*)-**5e** was prepared from geranyl acetate as a control substrate by the use of Scafato's methods.[19] Control substrate (*S*)-**5f** was prepared by the action of Grubbs catalyst **1** on (*S*)-**5d**, thereby inherently confirming the ability of the allyl group to function as a relay in this situation. Boronates (*S*)- and (*R*)-**5g** were also prepared from diols (*S*)- and (*R*)-**5b** by direct condensation with phenyl boronic acid in ethyl acetate. These latter substrates, now incorporating UV active chromophores, could be analyzed directly by HPLC for enantiomeric purity and were found to have identical enantiomeric excesses to benzoates (*S*)- and (*R*)-**5c** (see SI).

Scheme 3. Synthesis of various trisubstituted alkenes

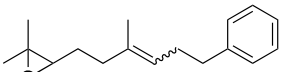
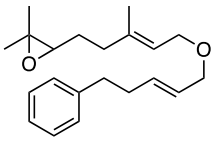
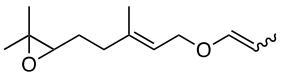
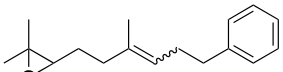
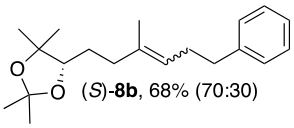
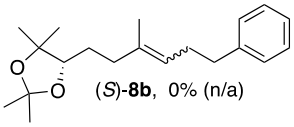
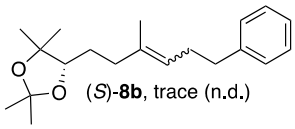
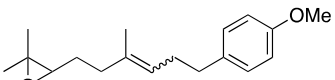
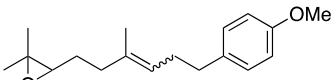
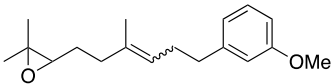


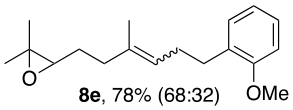
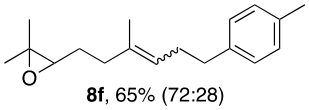
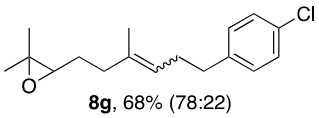
Attention now turned to the assembling a collection of suitable trisubstituted alkenes for this study. Trisubstituted alkenes **7a** and **7d-7k** were prepared by the Wittig reaction of isopropyl phosphonium iodide with aldehydes (Scheme 3).[20] Alternatively, trisubstituted alkene **7c** could be prepared by the reaction of the

corresponding benzylic Grignard reagent with prenyl bromide under Pd(0) catalysis.[3b] The former method is preferred, since non-perfect regioselectivity from competing S_N2' attack is possible in the latter. Prenyl acetone **7l** was commercially available, as was terminal alkene **7b** which was used for control experiments (*vide infra*).

With these substrates in hand we selected relay (*E*)-**5a** and trisubstituted alkene **7a** as the partner olefin to test in the proposed ReXM reaction. It is well established that trisubstituted olefins – classified as Type III olefins[21] – do not homodimerize, and this prompted us to use trisubstituted alkene **7a** in excess with the expectation that this would thereby help facilitate the desired cross metathesis. Although various attempts to mediate the proposed ReXM in toluene or dichloromethane solution failed, neat epoxide (*E*)-**5a** underwent smooth ReXM using 10 mol% **1** with trisubstituted alkene **7a** (5 equiv.) at 50 ˚C to provide functionalized epoxypolyene **8a** in excellent isolated yield (Table 1, entry 1). In stark contrast, the use of terminal olefin **7b** under the same conditions (entry 2) with epoxide (*E*)-**5a** gave instead direct cross metathesis product **9a** and isomerized vinyl ether **10a** as the major epoxide containing products, demonstrating that the use of a trisubstituted alkene is critical for these reactions. Control experiments with acetonides (S)-**5d-f** (entries 4-6)[22] verifies also the vital role of the relay in this ReXM process, and a comparison with the reaction with *Z*-epoxide (*Z*)-**5a** (entry 3) establishes the olefin geometry in the relay substrate as unimportant. Further examples of epoxides (*E*)- and (*Z*)-**5a** with various homoprenyl benzenes **7c-g** establishes the generality of the method (entries 7-12).[23] In all successful cases, the ReXM products **8a-g** were obtained with moderate *E*-olefin selectivity (*ca.* 2-3:1), as inseparable isomers, which is a limitation of the method.[24] However, these selectivities are directly comparable to those previously reported for the formation of trisubstituted olefins by cross metathesis with ruthenium benzylidene pre-catalysts (*c.f.* Figure 1, c, d).[10-12]

Table 1. ReXM of relay-actuated $\Delta^{6,7}$-functionalized monoterpenoids with homoprenyl benzenes using 10 mol% GII catalyst (**1**)[a]

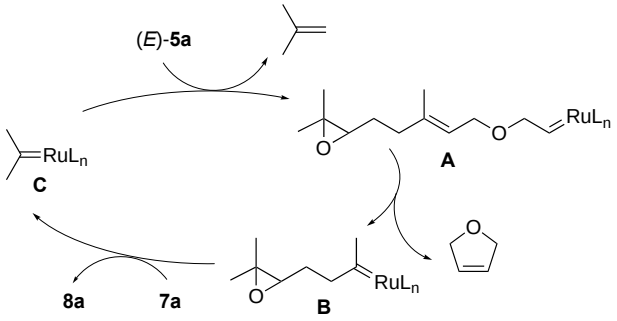
Entry[a]	Relay	Partner Olefin	Product[b-c]
1	(*E*)-**5a**	**7a**	 **8a**, 84% (73:27)
2	(*E*)-**5a**	**7b**	 **9a**, 37%  **10a**, 27% (49:51)[d]
3	(*Z*)-**5a**	**7a**	 **8a**, 69% (79:21)
4	(*S*)-**5d**	**7a**	 (*S*)-**8b**, 68% (70:30)
5	(*S*)-**5e**	**7a**	 (*S*)-**8b**, 0% (n/a)
6	(*S*)-**5f**	**7a**	 (*S*)-**8b**, trace (n.d.)
7	(*E*)-**5a**	**7c**	 **8c**, 66% (66:34)
8	(Z)-**5a**	**7c**	 **8c**, 60% (67:33)
9	(*E*)-**5a**	**7d**	 **8d**, 61% (72:28)

10	(*E*)-**5a**	**7e**	 **8e**, 78% (68:32)
11	(*E*)-**5a**	**7f**	 **8f**, 65% (72:28)
12	(*E*)-**5a**	**7g**	 **8g**, 68% (78:22)

[a] 0.25 mmol scale, conditions: olefin (5 equiv.), GII (**1**) (10 mol%), neat, 50 °C, 1 h; [b] Percentage isolated yields shown after chromatography; [c] Figures in parentheses are the *E/Z* ratio determined by ^{1}H NMR and assigned on the basis of characteristic ^{13}C NMR shielded methyl resonances for *E*-isomers (see experimental for details); [d] *E/Z* ratio determined by ^{1}H NMR and assigned on the basis of characteristic $^{3}J_{H\text{-}H}$ coupling constants.

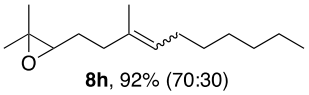
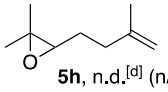
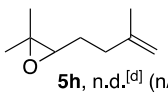
A possible catalytic cycle for this ReXM process using representative epoxide (*E*)-**5a** with homoprenyl benzene **7a**, invokes Diver[15] for the conversion of **A** to **B** with loss of dihydrofuran (Figure 2). The regioselective reactions of ruthenium species of type **B** with trisubstituted olefins have been proposed by Robinson,[12] which would produce the ReXM product **8a**, and ruthenium isopropylidene **C**. In this scenario, the catalytic cycle would be closed by re-initiation of ruthenium isopropylidene **C**[11] on the terminal olefin of relay epoxide (*E*)-**5a** with concomitant loss of isobutylene.[25] This mechanism is consistent also with the results obtained using nerol vs geraniol derived substrates (*c.f.*, Table 1, entries 1 vs 3 & entries 7 vs 8) since the same ruthenium alkylidene of the type **B**, should be formed after initial relay metathesis.

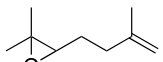
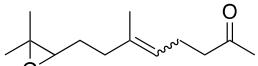
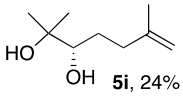
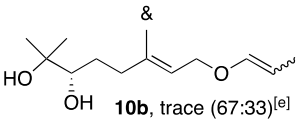
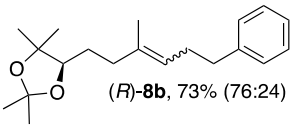
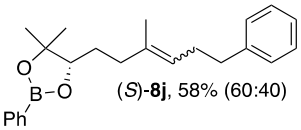
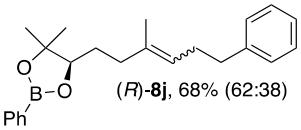
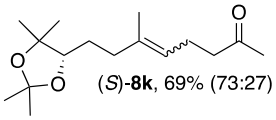
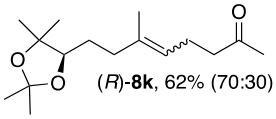
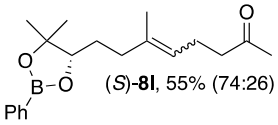
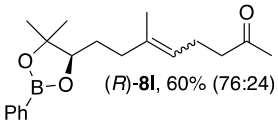
Figure 2. Possible catalytic cycle for the ReXM reaction.



With the ReXM method established for the reaction with homoprenyl benzenes, we explored further reactions with a variety of relay substrates and different trisubstituted alkenes as a general method for the functionalization of pre-existing trisubstituted olefins in acyclic monoterpenoid alcohols (Table 2). Thus, epoxide (*E*)-**5a** underwent smooth ReXM with aliphatic trisubstituted alkene **7h** to give ReXM product **8h** in excellent yield (Table 1, entry 1). α-Branching of the alkyl chain as in olefin **7i** (entry 2), proved to be detrimental to the process, where β,β-dimethylstyrene (**7j**) and prenylbenzene (**7k**) (entries 3-4) as partner olefins also failed – producing only truncated alkene **5h** – presumably on the basis of increased steric demand in each of these partner olefins. Readily available prenyl acetone **7l** gave the ReXM product **8i** (entry 5), but diol (*S*)-**5b** unexpectedly failed to undergo ReXM (entry 6), resulting in truncated compound **5i** and isomerized product **9b** (implicating catalyst decomposition to a ruthenium hydride species).[26] Acetonides (*S*)- & (*R*)-**5d** and boronates (*S*)- & (*R*)-**5g** however**,** participated cleanly in ReXM reactions (entries 7-13) to provide the desired products (*S*)- & (*R*)-**8b**, **8j-l** without complication. In these latter instances, these substrates are all derived from highly enantioselective Sharpless dihydroxylations of geranyl allyl ether [(*E*)-**4**, *vide infra*], thereby providing the ReXM adducts in uniformly high enantiomeric excess, which we flag as an advantage of this methodology.

Table 2. ReXM of relay-actuated $\Delta^{6,7}$-functionalized monoterpenes with various trisubstituted olefins using 10 mol% GII catalyst (**1**)[a]

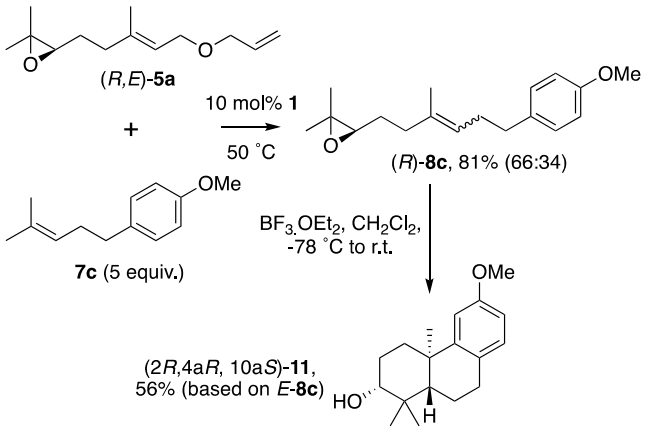
Entry[a]	Relay	Partner Olefin	Product[b-c]
1	(*E*)-**5a**	**7h**	 **8h**, 92% (70:30)
2	(*E*)-**5a**	**7i**	 **5h**, n.d.[d] (n/a)
3	(*E*)-**5a**	**7j**	 **5h**, n.d.[d] (n/a)

4	(*E*)-**5a**	**7k**	 **5h**, n.d.[d] (n/a)
5	(*E*)-**5a**	**7l**	 **8i**, 64% (73:27)
6	(*S*)-**5b**	**7a**	 **5i**, 24% (n/a) &  **10b**, trace (67:33)[e]
7	(*R*)-**5d**	**7a**	 (*R*)-**8b**, 73% (76:24)
8	(*S*)-**5g**	**7a**	 (*S*)-**8j**, 58% (60:40)
9	(*R*)-**5g**	**7a**	 (*R*)-**8j**, 68% (62:38)
10	(*S*)-**5d**	**7l**	 (*S*)-**8k**, 69% (73:27)
11	(*R*)-**5d**	**7l**	 (*R*)-**8k**, 62% (70:30)
12	(*S*)-**5g**	**7l**	 (*S*)-**8l**, 55% (74:26)
13	(*R*)-**5g**	**7l**	 (*R*)-**8l**, 60% (76:24)

[a] 0.25 mmol scale, conditions: olefin (5 equiv.), GII (**1**) (10 mol%), neat, 50 °C, 1 h; [b] Percentage isolated yields shown after chromatography; [c] Figures in parentheses are the *E/Z* ratio determined by ^{1}H NMR and assigned on the basis of characteristic ^{13}C NMR shielded methyl resonances for *E*-isomers (See experimental for details); [d] 'Truncated' compound **5h** was not isolated due to its volatility but assigned on the basis of a characteristic ^{1}H resonance at δ 4.72 (m, 2H) ppm; [e] *E/Z* ratio determined by ^{1}H NMR and assigned on the basis of characteristic $^{3}J_{H\text{-}H}$ coupling constants.

In order to overcome the inherent *E/Z* mixture limitation of this cross-metathesis method, we elected to demonstrate an epoxypolyene cyclization with the expectation that any resulting products would have more marked polarity differences. Accordingly, we prepared ReXM product (*R*)-**8c** from enantiomerically pure epoxide (*R*,*E*)-**5a** and homoprenyl methoxybenzene (**7c**) in good yield (81%) as an inseparable 2:1 *E*:*Z* mixture (Scheme 4). Boron trifluoride promoted epoxypolyene cyclization of this *E*/*Z* mixture provided single enantiomer podocarpane-type tricycle **11** (56% yield based on *E*-**8c**) as a single diastereoisomer which was readily separated away from the other components in the reaction mixture.[27] To the best of our knowledge, tricycle **11** has not previously been prepared in single enantiomer form,[28] thereby validating the utility of this two-step metathesis-cyclization sequence.[29]

Scheme 4. ReXM-epoxypolyene cyclization sequence.



Conclusion

In conclusion, we have designed and demonstrated a novel ruthenium benzylidene catalyzed relay cross metathesis ("ReXM") reaction for the preparation of podocarpane-type epoxypolyene cyclization substrates from relay-actuated $\Delta^{6,7}$-functionalized monoterpenoid alcohols with homoprenyl benzenes. It constitutes also a general method for the cross metathesis of pre-existing trisubstituted olefins in other relay-actuated $\Delta^{6,7}$-

functionalized monoterpenoid alcohols with various other trisubstituted alkenes to form new trisubstituted olefins, thereby facilitating the ability to valorize terpene biomass. The limitation inherent in the method regarding *E*/*Z* selectivity requires further advances in catalyst development to provide *E*- and *Z*-selective ruthenium benzylidene catalysts for trisubstituted olefins. However, in this situation, this can be overcome by cyclization of a *E*/*Z*-epoxypolyene substrate to give a separable, enantiomerically pure, podocarpane-type tricycle (from the *E*-geometrical isomer) in comparable yield to such cyclizations already reported in the literature.[2]

Experimental

Experimental Techniques: All reactions were carried out in oven-dried glassware. Air-sensitive reactions were performed under a positive pressure of nitrogen unless stated otherwise. Reaction temperatures other than room temperature were achieved using an oil bath, ice/water bath or a dry ice/acetone. 'Concentrated' refers to concentrating of the solution *in vacuo*. 'Chromatographed' refers to flash column chromatography on silica gel, particle size 33−70 μm or 40−63 μm, unless otherwise stated. 'DCVC' refers to dry column vacuum chromatography on silica gel, particle size 33−70 μm.[30] Analytical TLC was performed on silica gel 60 F254 pre-coated aluminium-backed plates and visualized with either irradiation with UV light (254 nm) or potassium permanganate, vanillin or phosphomolybdic acid staining. Brine refers to a saturated aqueous NaCl solution.

Characterization: Fourier transform infra-red (IR) spectra were recorded neat using an ATR-IR spectrometer and absorptions are reported to the nearest wavenumber. The (expected) very weak C=C and sp^2 C-H bond stretches for trisubstituted alkenes **7** and **8**, failed to be automatically pick peaked because they fell under the peak picking threshold, although they can be observed (in most cases) by careful inspection of the spectra.[29] ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker DRX-400 or Bruker AV-400. Chemical shifts (δ) are expressed in parts per million (ppm) relative to the residual solvent peak. ^{1}H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 101 MHz. NMR acquisitions were performed at 298

K unless stated otherwise. Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; qu., quintet; m, multiplet. High resolution mass spectrometry (HRMS) was conducted by the Imperial College Department of Chemistry Mass Spectrometry Service.

Reagents: Allyl bromide was distilled freshly before use, otherwise all reagents were obtained from commercial suppliers and used as received.

Solvents: All reactions were carried out in anhydrous solvents. HPLC grade CH_2Cl_2, THF, and EtOAc were dried by passing through a column of alumina beads. Extraction solvents, chromatography eluents (*n*-hexane, petrol, pentanes, CH_2Cl_2, Et_2O and EtOAc) and ^{t}BuOH, were used as received. 'Petrol' refers to petroleum ether (40 – 60 °C). Petroleum ether (40 – 60 °C), EtOAc, CH_2Cl_2 and Et_2O were GPR grade and pentanes were HPLC grade.

*(E)-1-(Allyloxy)-3,7-dimethylocta-2,6-diene [(E)-**4**]*.[17] Using a modified procedure of Rao and Senthilkumar, to a mixture of neat geraniol [(*E*)-**3**] (5.30 mL, 30 mmol, 1.0 equiv.), allyl bromide (7.8 mL, 90 mmol, 3.0 equiv.), and TBAI (554 mg, 1.50 mmol, 5 mol%) was added crushed KOH pellets (3.37 g, 60.0 mmol, 2.0 equiv.) at room temperature and the mixture was stirred for 18 h. The crude reaction mixture was purified by loading directly onto a pad of silica gel and eluting with *n*-hexane, to give allyl ether (*E*)-**4** (5.78 g, 29.7 mmol, 99%) as a colourless oil. 10.14469/hpc/5738. R_f 0.60 (*n*-hexane); IR (ATR, neat) 1670, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.39 – 5.33 (m, 1H), 5.27 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.18 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.13 – 5.06 (m, 1H), 4.00 (d, *J* = 6.8 Hz, 2H), 3.97 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.16 – 1.96 (m, 4H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.66 (s, 3H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.4, 135.2, 131.8, 124.2, 120.9, 117.1, 71.1, 66.7, 39.8, 26.5, 25.9, 17.8, 16.6; HRMS (EI^+) *m/z* calcd for $C_{13}H_{22}O$ $[M]^{\bullet+}$ 194.1671, found 194.1682.

*(E)-3-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane [(E)-**5a**].*[31] To a stirred solution of ether (*E*)-**4** (1.41 g, 7.28 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was added dropwise a solution of *m*CPBA (1.63 g, 77%, 7.28 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) over *ca.* 0.5 h at 0 °C. The mixture was allowed to warm to room temperature gradually. After a total reaction time of 18 h, the reaction mixture was concentrated, dissolved in EtOAc (100 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), brine (100 mL), dried over Na_2SO_4, concentrated and chromatographed (20-50% Et_2O in pentanes), to give epoxide (*E*)-**5a** (1.71 g, 8.1 mmol, 81%) as a colourless oil. 10.14469/hpc/5820. R_f 0.57 (30% EtOAc in pentanes); IR (ATR, neat) 3075, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.5, 10.5, 5.7 Hz, 1H), 5.43 – 5.36 (m, 1H), 5.26 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.5, 1.5 Hz, 1H), 3.99 (d, *J* = 6.8 Hz, 2H), 3.97 – 3.94 (m, 2H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.26 – 2.07 (m, 2H), 1.68 (s, 3H), 1.67 – 1.62 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.4, 135.1, 121.5, 117.2, 71.3, 66.7, 64.2, 58.5, 36.4, 27.3, 25.0, 18.9, 16.7; HRMS (CI^+) calcd for $C_{13}H_{21}O_2$ $[M - H]^+$ 209.1536, found 209.1535.

*(Z)-1-(Allyloxy)-3,7-dimethylocta-2,6-diene [(Z)-**4**]*.[17] Using a modified procedure of Rao and Senthilkumar, to a neat mixture of nerol [(*Z*)-**3**] (5.30 mL, 30 mmol, 1.0 equiv), allyl bromide (7.8 mL, 90 mmol, 3.0 equiv) and TBAI (554 mg, 1.50 mmol, 5 mol%) was added crushed KOH pellets (3.37 g, 60.0 mmol, 2.0 equiv) at room temperature and the mixture was stirred for 18 h. The crude reaction mixture was purified by loading directly onto a pad of silica gel and eluting with *n*-hexane, to give allyl ether (*Z*)-**4** (5.81 g, 29.9 mmol, quant.) as a colourless oil. 10.14469/hpc/5741. R_f 0.65 (*n*-hexane); IR (ATR, neat) 3091, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.3, 10.3, 5.6 Hz, 1H), 5.41 – 5.32 (m, 1H), 5.30 – 5.24 (m, 1H), 5.21 – 5.13 (m, 1H), 5.14 – 5.04 (m, 1H), 4.00 – 3.92 (m, 4H), 2.12 – 2.02 (m, 4H), 1.75 (d, *J* = 1.2 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.5, 135.2, 132.0, 124.0, 122.0, 116.9, 71.1, 66.4, 32.4, 26.8, 25.8, 23.6, 17.7; HRMS (EI^+) *m/z* calcd for $C_{13}H_{22}O$ $[M]^{\bullet+}$ 194.1671, found 194.1670.

*(Z)-3-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane [(Z)-**5a**]*. To a stirred solution of ether (*Z*)-**4** (1.41 g, 7.28 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was added dropwise a solution of *m*CPBA (1.63 g, 77%,

7.28 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) over *ca.* 0.5 h at 0 °C, the mixture was allowed to warm to room temperature gradually. After a total reaction time of 18 h, the reaction mixture was concentrated, dissolved in EtOAc (100 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), brine (100 mL), dried over Na_2SO_4, concentrated and chromatographed (20-50% Et_2O in pentanes), to give epoxide (*Z*)-**5a** (1.60 g, 7.6 mmol, 76%) as a colourless oil. 10.14469/hpc/5742. R_f 0.25 (10% EtOAc in *n*-hexane); IR (ATR, neat) 3075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.46 – 5.38 (m, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.03 – 3.93 (m, 4H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.29 – 2.15 (m, 2H), 1.76 (d, *J* = 1.2 Hz, 3H), 1.71 – 1.54 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.6, 135.0, 122.5, 117.1, 71.3, 66.3, 64.0, 58.5, 29.0, 27.6, 25.0, 23.5, 18.8; HRMS (ES^+) *m/z* calcd for $C_{13}H_{21}O_2$ $[M - H]^+$ 209.1542, found 209.1547.

*(S,E)-8-(Allyloxy)-2,6-dimethyloct-6-ene-2,3-diol [(S)-**5b**]*.[31] Using a modified procedure of Sharpless,[18] to a vigorously stirred solution of AD-mix-α (7.0 g, 1.4 g mol^{-1}) in ^{t}BuOH (75 mL) and H_2O (75 mL) was added $MeSO_2NH_2$ (476 mg, 5.0 mmol, 1.0 equiv.) followed by ether (*E*)-**4** (972 mg, 5.0 mmol, 1.0 equiv.). The reaction mixture was allowed to stir for 16 h, the mixture was quenched by the addition of a 20% Na_2SO_3 aqueous solution (150 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$, concentrated and chromatographed (40% EtOAc in *n*-hexane), to give diol (*S*)-**5b** (632 mg, 2.8 mmol, 55%) as a colourless oil. 10.14469/hpc/5743. R_f 0.36 (40% EtOAc in *n*-hexane); $[\alpha]_D^{20}$ -26.1 (*c* 1.0, $CHCl_3$); IR (ATR, neat) 3600-3100, 3075, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.47 – 5.37 (m, 1H), 5.28 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.03 – 3.93 (m, 4H), 3.36 (dd, *J* = 10.5, 2.0 Hz, 1H), 2.31 (ddd, *J* = 14.7, 9.7, 5.2 Hz, 1H), 2.16 – 2.06 (m, 1H), 1.99-1.81 (br s, 2H), 1.68 (s, 3H), 1.66 – 1.56 (m, 1H), 1.51 – 1.39 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.3, 135.1, 121.4, 117.3, 78.3, 73.3, 71.4, 66.7, 36.8, 29.7, 26.7, 23.4, 16.7; HRMS (ES^+) calcd for $C_{13}H_{24}O_3Na$ $[M + Na]^+$ 251.1623, found 251.1631. *(R,E)-8-(Allyloxy)-2,6-dimethyloct-*

*6-ene-2,3-diol [(R)-**5b**]* was prepared under identical conditions but using AD-mix-β. $[\alpha]_D^{20}$ + 26.1 (*c* 1.0, $CHCl_3$).

*(R,E)-3-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane [(R,E)-**5a**]*.[31] To a solution of diol (*S*)-**5b** (208 mg, 0.91 mmol, 1.0 equiv.) in CH_2Cl_2 (1.8 mL) at 0 ˚C was added MsCl (0.11 mL, 1.4 mmol, 1.5 equiv.) followed by pyridine (0.59 mL, 7.3 mmol, 8.0 equiv.) dropwise. The reaction mixture was allowed to gradually warm to room temperature and was stirred for 20 h, after which the mixture was poured into a suspension of K_2CO_3 (1.9 g, 14 mmol, 15 equiv.) in MeOH (9 mL). This suspension was stirred for a further 18 h. The reaction mixture was then concentrated, diluted with H_2O (80 mL) and extracted with EtOAc (3 × 40 mL). The combined organics were washed with a saturated aqueous $CuSO_4$ solution (3 × 50 mL), then brine (50 mL), dried over Na_2SO_4, concentrated and chromatographed (5-10% EtOAc in petrol), to give epoxide (*R,E)*-**5a** (171 mg, 0.81 mmol, 89%) as a colourless oil. R_f 0.57 (30% EtOAc in pentanes); $[\alpha]_D^{22}$ + 4.1 (*c* 1.0, $CHCl_3$). Data is otherwise identical to the racemic material (*E*)-**5a**.

*(S,E)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl benzoate [(S)-**5c**]*. To a solution of diol (*S*)-**5b** (25.0 mg, 0.11 mmol, 1.0 equiv.) in pyridine (1 mL) was added benzoyl chloride (16 µL, 0.14 mmol, 1.3 equiv.) and the reaction mixture was stirred at room temperature for 18 h. Then was added additional benzoyl chloride (33 µL, 0.28 mmol, 2.6 equiv.) and the mixture was stirred for an additional 5 h. The reaction mixture was diluted with EtOAc (25 mL) and washed with a 1M aqueous HCl solution (3 × 20 mL) and a saturated aqueous $NaHCO_3$ solution (3 × 20 mL). The organics were dried over Na_2SO_4, concentrated and chromatographed on silica gel (20% EtOAc in *n*-hexane), to give benzoate (*S*)-**5c** (33.0 mg, 0.11 mmol, 99%) as a colourless oil. 10.14469/hpc/5744. R_f 0.41 (40% EtOAc in *n*-hexane); $[\alpha]_D^{20}$ - 16.7 (*c* 1.0, $CHCl_3$); IR (ATR, neat) 3600-3250, 3064, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 2H), 7.63 – 7.54 (m, 1H), 7.50 – 7.42 (m, 2H), 5.91 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.38 – 5.30 (m, 1H), 5.30 – 5.22 (m, 1H), 5.20 – 5.14 (m, 1H), 5.07 (dd, *J* = 9.6, 3.3 Hz, 1H), 4.01 – 3.86 (m, 4H), 2.13 – 2.03 (m, 2H), 1.98 – 1.74 (m, 3H), 1.65 (s, 3H), 1.27 (s, 6H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.8, 139.4, 135.1, 133.3, 130.2, 129.8, 128.6, 121.4, 117.1, 80.4, 72.8, 71.2, 66.6, 36.1, 27.9, 26.7, 25.3, 16.7; HRMS (ES^+) calcd for $C_{20}H_{28}O_4Na$ $[M + Na]^+$ 355.1885, found 355.1894. HPLC (CHIRALCEL OD; 10% IPA in *n*-hexane; 0.5 mL/min) t_R = 10.1 min (major), 10.9 min (minor) (96:4). *(R,E)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl benzoate [(R)-**5c**]* was prepared under identical conditions from diol (*R*)-**5b**. $[\alpha]_D^{31}$ + 12.4 (*c* 0.8, $CHCl_3$). HPLC (CHIRALCEL OD; 10% IPA in *n*-hexane; 0.5 mL/min) t_R = 9.9 min (minor), 10.6 min (major) (4:96).

*(S,E)-5-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2,4,4-tetramethyl-1,3-dioxolane [(S)-**5d**]*. To a solution of diol (*S*)-**5b** (1.05 g, 4.59 mmol, 1.0 equiv.) in CH_2Cl_2 (9 mL) were added dimethoxypropane (5.60 mL, 45.9 mmol, 10.0 equiv.) and pyridinium *p*-toluenesulfonate (577 mg, 2.30 mmol, 0.5 equiv.) at room temperature and the mixture was stirred for 18 h. The reaction mixture was concentrated and loaded directly onto a column of silica gel and chromatographed (5-10% EtOAc in petrol) to give acetonide (*S*)-**5d** (1.11 g, 4.13 mmol, 90%) as a colourless oil. 10.14469/hpc/5745. R_f 0.23 (5% EtOAc in petrol); $[\alpha]_D^{24}$ 2.1 (*c* 1.0, $CHCl_3$); IR (ATR, neat) 3075, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 – 5.86 (m, 1H), 5.44 – 5.35 (m, 1H), 5.27 (br d, *J* = 17.2 Hz, 1H), 5.17 (br d, *J* = 10.4 Hz, 1H), 3.99 (d, *J* = 6.8 Hz, 2H), 3.96 (d, *J* = 5.7 Hz, 2H), 3.65 (dd, *J* = 9.5, 3.3 Hz, 1H), 2.34 – 2.20 (m, 1H), 2.13 – 2.00 (m, 1H), 1.68 (s, 3H), 1.69 – 1.58 (m, 1H), 1.56 – 1.43 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 1.08 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 139.6, 135.0, 121.1, 117.0, 106.5, 82.9, 80.1, 71.1, 66.5, 36.7, 28.6, 27.5, 26.9, 26.1, 22.9, 16.6; HRMS (EI^+) *m/z* calcd for $C_{16}H_{28}O_3$ $[M]^{\bullet+}$ 268.2038, found 268.2050. *(R,E)-5-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2,4,4-tetramethyl-1,3-dioxolane [(R)-**5d**]* was prepared under identical conditions from diol (*R*)-**5b**. $[\alpha]_D^{24}$ -1.5 (*c* 1.0, $CHCl_3$).

*(S)-2,2,4,4-Tetramethyl-5-(3-methylbut-3-en-1-yl)-1,3-dioxolane [(S)-**5f**]*. To a solution of (*S*,*E*)-acetonide (*S*)-**5d** (100 mg, 0.37 mmol, 1.0 equiv.) in CH_2Cl_2 (37 mL) was added ruthenium benzylidene **1** (3.2 mg, 0.0037 mmol, 1 mol%). The mixture was heated to reflux with stirring for 2 h. The reaction mixture was concentrated and loaded directly onto a column of silica gel and chromatographed (5% EtOAc in petrol) to give alkene (*S*)-

5f (57 mg, 0.28 mmol, 77%) as a colourless oil. 10.14469/hpc/5755. R_f 0.53 (5% EtOAc in petrol); $[\alpha]_D^{24}$ - 1.4 (*c* 1.0, $CHCl_3$); IR (ATR, neat) 3071, 1648 cm^{-1}; ^1H NMR (400 MHz, CDCl) δ 4.74 (s, 1H), 4.71 (s, 1H), 3.68 (dd, *J* = 9.4, 3.5 Hz, 1H), 2.31 – 2.17 (m, 1H), 2.12 – 2.00 (m, 1H), 1.74 (s, 3H), 1.71 – 1.60 (m, 1H), 1.57 – 1.46 (m, 1H), 1.42 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 145.2, 110.1, 106.5, 82.8, 80.1, 34.9, 28.6, 27.4, 26.9, 26.0, 22.9, 22.6; HRMS (EI^+) *m/z* calcd for $C_{12}H_{22}O_2$ $[M]^{\bullet+}$ 198.1620, found 198.1612.

*(S,E)-5-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-4,4-dimethyl-2-phenyl-1,3,2-dioxaborolane [(S)-**5g**]*. Phenylboronic acid (315 mg, 2.63 mmol, 1.05 equiv.) was added to a solution of diol (*S*)-**5b** (570 mg, 2.5 mmol, 1 equiv.) in EtOAc (10 mL). After 90 min the reaction mixture was concentrated, passed through a silica plug (15% EtOAc in petrol; 150 mL) and evaporated to give boronate (*S*)-**5g** (775 mg, 2.50 mmol, 99%) as a pale beige viscous oil. 10.14469/hpc/6317. $[\alpha]_D^{25}$ -17.1 (*c* 1.0, $CHCl_3$); IR (ATR, neat) 3075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.51 – 7.42 (m, 1H), 7.41 – 7.33 (m, 2H), 6.00 – 5.89 (m, 1H), 5.46 (t, *J* = 6.6 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 4.06 (dd, *J* = 10.3, 3.4 Hz, 1H), 4.02 (d, *J* = 6.7 Hz, 2H), 3.99 (d, *J* = 5.7 Hz, 2H), 2.48 – 2.38 (m, 1H), 2.23 – 2.12 (m, 1H), 1.81 – 1.69 (m, 1H), 1.73 (s, 3H), 1.68 – 1.59 (m, 1H), 1.44 (s, 3H), 1.29 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.6, 135.0, 134.8, 131.3, 127.8, 121.2, 117.1, 85.3, 82.1, 71.2, 66.6, 36.4, 29.9, 28.8, 23.5, 16.7; MS (EI^+) *m/z* calcd for $C_{19}H_{27}{}^{11}BO_3$ $[M]^{\bullet+}$ 314.2053, found 314.2062. HPLC (CHIRALCEL OD-H, 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 8.5 min (major), 10.8 min (minor) (95:5). *(R,E)-5-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-4,4-dimethyl-2-phenyl-1,3,2-dioxaborolane [(R)-**5g**]* was prepared under identical conditions from diol (*R*)-**5b**. $[\alpha]_D^{25}$ +15.8 (*c* 1.0, $CHCl_3$). HPLC (CHIRALCEL OD-H, 1% IPA in *n*-hexane; 1.0 mL/min) t_R = 8.5 min (minor), 10.8 min (major) (3:97).

General procedure for preparation of trisubstituted alkenes 7 via Wittig olefination of aldehydes. Using a modified procedure of Pfaltz,[20] to suspension of $(CH_3)_2CHPPh_3I$ **6** (7.8 g, 18 mmol, 1.8 equiv.) in THF (20

mL) was added ^{n}BuLi (11.25 mL, 1.6 M in hexanes, 18 mmol, 1.8 equiv.) dropwise at 0 °C. After 30 min, the required aldehyde (1.0 equiv.) was added dropwise and the mixture was stirred for 18 h. The mixture was quenched by addition of H_2O (15 mL) and the THF was removed by concentration. The mixture was diluted with Et_2O (100 mL) and filtered through a pad of Celite. The organics were washed with H_2O (3 × 20 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by DCVC, eluting with pentanes, to give the desired trisubstituted alkene.

*(4-Methylpent-3-en-1-yl)benzene (**7a**).*[32] Following the general procedure for the formation of trisubstituted alkenes using hydrocinnamaldehyde (1.32 mL, 10.0 mmol, 1.0 equiv.) gave alkene **7a** (0.99 g, 6.1 mmol, 61%) as a colourless oil. 10.14469/hpc/5759. R_f 0.44 (pentanes); IR (ATR, neat) 3027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 2H), 7.22 – 7.12 (m, 3H), 5.24 – 5.09 (m, 1H), 2.68 – 2.58 (m, 2H), 2.29 (q, *J* = 7.7 Hz, 2H), 1.68 (s, 3H), 1.56 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 142.5, 132.3, 128.6, 128.3, 125.8, 123.9, 36.3, 30.2, 25.8, 17.8; HRMS (CI^{+}) *m/z* calcd for $C_{12}H_{17}$ $[M + H]^{+}$ 161.1330, found 161.1325.

*1-Methoxy-4-(4-methylpent-3-en-1-yl)benzene (**7c**).*[3b] To a solution of *p*-methoxybenzyl chloride (2.26 mL, 16.6 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise over 20 min to magnesium turnings (0.478 g , 20.0 mmol, 1.2 equiv.) in THF (10 mL) and at 0°C. The reaction was warmed to room temperature and the mixture was stirred for 3 h. To the mixture was added dropwise a solution of tetrakis(triphenylphosphine)palladium(0) (0.226 g, 0.196 mmol, 1.5 mol%) and 1-bromo-3-methylbut-2-ene (2.4 mL, 20.1 mmol, 1.0 equiv.) in THF (10 mL) at -78°C. The reaction mixture turned to green immediately and was stirred for an additional 3 h before warming to room temperature. The reaction mixture was stirred for 16 h and quenched with ice water (20 mL), extracted with Et_2O (2 × 20 mL). The organics were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated and chromatographed (20% EtOAc in *n*-hexane) to give alkene **7c** (2.29 g, 12.3 mmol, 70%, containing 5% of inseparable *p*-methoxytoluene). 10.14469/hpc/5761. R_f 0.20 (10% EtOAc in *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.18 (t, *J* = 7.1, 1H), 3.80 (s, 3H), 2.58 (t, *J* = 7.8 Hz, 2H), 2.27 (app. q, *J* = 7.8 Hz,

2H), 1.70 (s, 3H), 1.58 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 157.7, 134.6, 132.1, 129.3, 123.8, 113.6, 55.3, 35.2, 30.3, 25.7, 17.7; HRMS (CI^+) calcd for $C_{13}H_{17}O$ $[M - H]^+$ 189.1274, found 189.1272.

*1-Methoxy-3-(4-methylpent-3-en-1-yl)benzene (**7d**)*. Following the general procedure for the formation of trisubstituted alkenes using $(CH_3)_2CHPPh_3I$ **6** (3.8 g, 8.8 mmol, 1.8 equiv.), THF (10 mL), ^{n}BuLi (3.5 mL, 2.5 M in hexanes, 8.8 mmol, 1.8 equiv) and 3-(3-methoxyphenyl)propanal[33] (0.8 g, 4.9 mmol, 1.0 equiv.) gave alkene **7d** (0.55 g, 59%) as a colourless oil. 10.14469/hpc/6318. R_f 0.85 (10% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.15 (m, 1H), 6.82 – 6.77 (m, 1H), 6.76 – 6.72 (m, 2H), 5.23 – 5.12 (m, 1H), 3.80 (s, 3H), 2.71 – 2.57 (m, 2H), 2.29 (app. q, *J* = 7.6 Hz, 2H), 1.69 (d, *J* = 1.3 Hz, 3H), 1.58 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 159.7, 144.2, 132.2, 129.3, 123.8, 121.0, 114.3, 111.1, 55.2, 36.3, 30.0, 25.8, 17.8; HRMS (CI^+) calcd for $C_{13}H_{19}O$ $[M + H]^+$ 191.1430, found 191.1430.

*1-Methoxy-2-(4-methylpent-3-en-1-yl)benzene (**7e**).*[34] Following the general procedure for the formation of trisubstituted alkenes using $(CH_3)_2CHPPh_3I$ **6** (3.9 g, 9.0 mmol, 1.8 equiv.), THF (10 mL), ^{n}BuLi (3.6 mL, 2.5 M in hexanes, 9.0 mmol, 1.8 equiv) and 3-(2-methoxyphenyl)propanal[35] (0.82 g, 5.0 mmol, 1.0 equiv.) gave alkene **7e** (0.73 g, 3.8 mmol, 76%) as a colourless oil. 10.14469/hpc/6319. R_f 0.20 (5% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.10 (m, 2H), 6.92 – 6.81 (m, 2H), 5.21 (m, 1H), 3.83 (s, 3H), 2.68 – 2.57 (m, 2H), 2.31 – 2.20 (m, 2H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.58 (d, *J* = 1.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 157.5, 131.8, 130.8, 129.8, 126.9, 124.3, 120.3, 110.2, 55.3, 30.6, 28.3, 25.7, 17.6; MS (CI^+) *m/z* calcd for $C_{13}H_{19}O$ $[M+H]^+$ 191.1430, found 191.1431.

*1-Methyl-4-(4-methylpent-3-en-1-yl)benzene (**7f**).*[36] Following the general procedure for the formation of trisubstituted alkenes using $(CH_3)_2CHPPh_3I$ **6** (2.5 g, 5.8 mmol, 1.2 equiv.), THF (10 mL), ^{n}BuLi (2.3 mL, 2.5 M in hexanes, 5.8 mmol, 1.2 equiv) and 3-(4-methylphenyl)propanal[37] (0.72 g, 4.9 mmol, 1.0 equiv.) gave alkene **7f** (0.51 g, 2.9 mmol, 60%) as a colourless oil. 10.14469/hpc/6320. R_f 0.93 (10% EtOAc in petrol); IR (ATR, neat) 3042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 4H), 5.26 – 5.12 (m, 1H), 2.66 – 2.56 (m, 2H),

2.33 (s, 3H), 2.29 (app. q, J = 7.7 Hz, 2H), 1.70 (s, 3H), 1.59 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 139.5, 135.2, 132.2, 129.1, 128.4, 124.0, 35.8, 30.3, 25.8, 21.2, 17.8; HRMS (EI^+) calcd for $C_{13}H_{18}$ $[M]^{\bullet+}$ 174.1409, found 174.1411.

*1-Chloro-4-(4-methylpent-3-en-1-yl)benzene (**7g**).*[38] Following the general procedure for the formation of trisubstituted alkenes using $(CH_3)_2CHPPh_3I$ **6** (3.9 g, 9.0 mmol, 1.8 equiv.), THF (10 mL), ^{n}BuLi (3.6 mL, 2.5 M in hexanes, 9.0 mmol, 1.8 equiv) and 3-(4-chlorophenyl)propanal[39] (843 mg, 5.0 mmol, 1.0 equiv.) gave alkene **7g** (828 mg, 4.3 mmol, 85%) as a colourless oil. 10.14469/hpc/6321. R_f 0.30 (5% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 2H), 7.13 – 7.08 (m, 2H), 5.13 (m, 1H), 2.63 – 2.56 (m, 2H), 2.31 – 2.22 (m, 2H), 1.68 (d, J = 1.4 Hz, 3H), 1.54 (d, J = 1.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 140.8, 132.5, 131.4, 129.8, 128.3, 123.3, 35.4, 29.9, 25.7, 17.7; MS (CI^+) *m/z* calcd for $C_{12}H_{14}{}^{35}Cl$ $[M-H]^+$ 193.0779, found 193.0777.

*2-Methylnon-2-ene (**7h**).*[40] Following the general procedure for the formation of trisubstituted alkenes using heptanal (1.40 mL, 10.0 mmol, 1.0 equiv.) gave alkene **7h** (0.59 g, 4.2 mmol, 42%) as a colourless oil. 10.14469/hpc/5756. R_f 0.94 (pentanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 – 5.01 (m, 1H), 2.03 – 1.88 (m, 2H), 1.69 (d, J = 1.4 Hz, 3H), 1.60 (s, 3H), 1.36 – 1.23 (m, 8H), 0.89 (t, J = 6.7 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 131.2, 125.1, 32.0, 30.0, 29.2, 28.2, 25.9, 22.8, 17.8, 14.3; HRMS (EI^+) calcd for $C_{10}H_{20}$ $[M]^{\bullet+}$ 140.1560, found 140.1554.

*4-Ethyl-2-methyloct-2-ene (**7i**).* Following the general procedure for the formation of trisubstituted alkenes using 2-ethylhexanal (1.56 mL, 10.0 mmol, 1.0 equiv.) gave alkene **7i** (0.87 g, 5.7 mmol, 57%) as a colourless oil. 10.14469/hpc/5760. R_f 0.92 (pentanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (br d, J = 9.8 Hz, 1H), 2.13 – 2.01 (m, 1H), 1.71 (d, J = 1.4 Hz, 3H), 1.60 (d, J = 1.3 Hz, 3H), 1.45 – 1.06 (m, 8H), 0.87 (t, J = 7.1 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 130.8, 130.4, 39.8, 35.8, 29.8, 29.0, 26.0, 23.1, 18.4, 14.3, 11.9; HRMS (EI^+) calcd for $C_{11}H_{22}$ $[M]^{\bullet+}$ 154.1721, found 154.1716.

*(2-Methylprop-1-en-1-yl)benzene (**7j**).*[20] Following the general procedure for the formation of trisubstituted alkenes using benzaldehyde (1.02 mL, 10.0 mmol, 1.0 equiv.) gave alkene **7j** (1.30 g, 9.8 mmol, 98%) as a colourless oil. 10.14469/hpc/5757. R_f 0.58 (pentanes); IR (ATR, neat) 3021, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.28 – 7.15 (m, 3H), 6.29 (s, 1H), 1.93 (s, 3H), 1.88 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.9, 135.6, 128.9, 128.2, 125.9, 125.3, 27.0, 19.6; HRMS (EI^+) calcd for $C_{10}H_{12}$ $[M]^{\bullet+}$ 132.0934, found 132.0933.

*(3-Methylbut-2-en-1-yl)benzene (**7k**).*[41] Following the general procedure for the formation of trisubstituted alkenes using phenylacetaldehyde (1.17 mL, 10.0 mmol, 1.0 equiv.) gave alkene **7k** (0.40 g, 2.8 mmol, 28%) as a colourless oil. 10.14469/hpc/5758. R_f 0.63 (pentanes); IR (ATR, neat) 3027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.22 – 7.13 (m, 3H), 5.40 – 5.27 (m, 1H), 3.35 (d, J = 7.4 Hz, 2H), 1.75 (d, J = 1.4 Hz, 3H), 1.72 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.9, 132.6, 128.5, 128.4, 125.8, 123.3, 34.5, 25.9, 17.9; HRMS (EI^+) calcd for $C_{11}H_{14}$ $[M]^{\bullet+}$ 146.1090, found 146.1084.

General procedure for preparation of trisubstituted alkenes 8 via relay cross metathesis. To a neat mixture of relay alkene **5** (0.25 mmol, 1.0 equiv.) and alkene **7** (1.25 mmol, 5.0 equiv.) was added ruthenium benzylidene **1** (21 mg, 0.025 mmol, 10 mol%). The mixture was heated to 50 °C for 1 h under a strong positive pressure of N_2 (g) *via* a needle in/out to aid the removal of volatiles. The resulting mixture was loaded directly onto a column of silica gel and chromatographed.

*2,2-Dimethyl-3-(3-methyl-6-phenylhex-3-en-1-yl)oxirane (**8a**).*[2a] Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)-**5a** (53 mg) and alkene **7a** (200 mg) gave trisubstituted alkene **8a** (51 mg, 0.21 mmol, 84% from (*E*)-**5a**; 42 mg, 0.17 mmol, 69% from (*Z*)-**5a**) as a colourless oil and a mixture of *E*/*Z* geometrical isomers [*E*/*Z* = 73:27 (from (*E*)-**5a**) or 79:21 (from (*Z*)-**5a**)]. 10.14469/hpc/5763. R_f 0.50 (10% EtOAc in pentanes); IR (ATR, neat) 3026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 7.20 – 7.12 (m, 3H), 5.25 – 5.18 (m, 1H), 2.72 – 2.59 (m, 3H), 2.37 – 2.26 (m, 2H), 2.20 – 2.01 (m, 2H), 1.71 – 1.52

(m, 5H), 1.28 (s, 3H), 1.24 (s, *E*-**8a**, 2.19H), 1.24 (s, *Z*-**8a**, 0.81H). The *E:Z* ratio was determined by integration of the resonances at δ 1.24(4) (major) and 1.23(9) (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 142.4, 142.3, 135.0, 135.0, 128.6, 128.4, 128.4, 125.9, 125.9, 125.2, 124.4, 64.3, 64.2, 58.5, 58.5, 36.5, 36.4, 36.2, 30.1, 30.0, 28.7, 27.6, 27.5, 25.1, 25.1, 23.5, 18.9, 18.9, 16.1. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.1 vs 23.5 ppm for the minor *Z*-isomer; HRMS (CI^+) calcd for $C_{17}H_{25}O$ $[M + H]^+$ 245.1905, found 245.1900.

*((E)-6-(((E)-3,7-Dimethylocta-2,6-dien-1-yl)oxy)hex-4-en-1-yl)benzene (**9a**) and 2,2-dimethyl-3-((3E)-3-methyl-5-(prop-1-en-1-yloxy)pent-3-en-1-yl)oxirane (**10a**).* Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)-**5a** (53 mg) and alkene **7b** (165 mg), with regular addition of **7b** at 10 min intervals to keep the reaction volume constant throughout the whole reaction process, gave first **10a** (14.3 mg, 0.07 mmol, 27%) as a colourless oil and a mixture of *E*/*Z* geometrical isomers [*E*/*Z* = 49:51], and second **9a** (29.0 mg, 0.09 mmol, 37%) as a colourless oil. **9a**: 10.14469/hpc/6466. R_f 0.30 (10% EtOAc in pentanes); IR (ATR, neat) 3023, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.80 – 5.70 (m, 1H), 5.66 – 5.56 (m, 1H), 5.42 – 5.35 (m, 1H), 3.95 (d, *J* = 6.8, 2H), 3.91 (dd, *J* = 6.0, 0.9 Hz, 2H), 2.71 (m, 3H), 2.38 (m, 2H), 2.27 – 2.07 (m, 2H), 1.71 – 1.62 (m, 5H), 1.30 (s, 3H), 1.26 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 141.9, 139.1, 133.7, 128.4, 128.3, 127.1, 125.8, 121.5, 70.8, 66.3, 64.0, 58.4, 36.2, 35.5, 34.1, 27.2, 24.9, 18.7, 16.5. HRMS (CI^+) calcd for $C_{21}H_{31}O_2$ $[M + H]^+$ 315.2319, found 315.2323. **10a**: 10.14469/hpc/6469. R_f 0.60 (10% EtOAc in pentanes); IR (ATR, neat) 1662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (dq, *J* = 12.5, 1.6 Hz, 0.51H, (*E*)-**9a**), 5.96 (dq, *J* = 6.3, 1.7 Hz, 0.49H, (*Z*)-**9a**), 5.41 (m, 1H), 4.79 (dq, *J* = 13.3, 6.7 Hz, 0.51H, (*E*)-**9a**), 4.38 (appr. qu., *J* = 6.8 Hz, 0.49H, (*Z*)-**9a**), 4.26 (d, *J* = 6.7 Hz, 1.02H, (*E*)-**9a**), 4.18 (d, *J* = 6.7 Hz, 0.98H, (*Z*)-**9a**), 2.70 (t, *J* = 6.3 Hz, 1H), 2.28 – 2.07 (m, 2H), 1.73 – 1.60 (m, 5H), 1.57 (dd, *J* = 6.8, 1.7 Hz, 1.53H, (*E*)-**9a**), 1.55 (dd, *J* = 6.7, 1.6 Hz, 1.47H, (*Z*)-**9a**), 1.30 (s, 3H), 1.26 (d, *J* = 1.7 Hz, 3H). The *E:Z* ratio was determined by integration of the resonances at δ 4.26 (major) and 4.18 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 146.2, 145.1, 139.8, 139.7, 128.5, 121.0, 120.4, 101.2, 98.8, 68.2,

65.7, 64.0, 58.4, 36.2, 36.2, 27.1, 24.9, 18.8, 16.6, 12.7, 9.3. HRMS (CI^+) calcd for $C_{13}H_{23}O_2$ $[M + H]^+$ 211.1693, found 211.1694.

*(S)-2,2,4,4-Tetramethyl-5-(3-methyl-6-phenylhex-3-en-1-yl)-1,3-dioxolane [(S)-**8b**]*. Following the general procedure for relay cross metathesis using acetonide (*S*)-(**5d**) (67 mg) and alkene **7a** (200 mg) gave trisubstituted alkene (*S*)-**8b** (51 mg, 0.17 mmol, 68%) as a light brown oil and a mixture of *E*/*Z* geometrical isomers (*E*/*Z* = 70:30). 10.14469/hpc/6326. R_f 0.58 (5% EtOAc in petrol); IR (ATR, neat) 3023 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.15 (m, 3H), 5.29 – 5.20 (m, 1H), 3.66 (dd, *J* = 9.3, 3.5 Hz, *E*-**8b**, 0.70H), 3.62 (dd, J = 9.6, 3.3 Hz, *Z*-**8b**, 0.30H), 2.70 – 2.61 (m, 2H), 2.38 – 2.27 (m, 2H), 2.27 – 2.10 (m, 1H), 2.09 – 1.96 (m, 1H), 1.74 – 1.68 (m, *Z*-**8b**, 0.90H), 1.67 – 1.59 (m, 1H), 1.58 (s, *E*-**8b**, 2.10H), 1.53 – 1.42 (m, 1H), 1.43 (s, *E*-**8b**, 2.10H), 1.43 (s, *Z*-**8b**, 0.90H), 1.33 (s, *E*-**8b**, 2.10H), 1.32 (s, *Z*-**8b**, 0.90H), 1.24 (s, *E*-**8b**, 2.10H), 1.23 (s, *Z*-**8b**, 0.90H), 1.11 (s, *E*-**8b**, 2.10H), 1.08 (s, *Z*-**8b**, 0.90H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.11 (major) and 1.08 (minor) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.3, 135.1, 128.5, 128.2, 125.7, 125.2, 124.1, 106.5, 82.8, 82.7, 80.1, 80.1, 36.7, 36.3, 36.1, 29.9, 29.8, 28.9, 28.6, 28.6, 27.8, 27.6, 26.9, 26.1, 23.3, 22.9, 16.0. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.0 vs 23.3 ppm for the minor *Z*-isomer; HRMS (EI^+) *m/z* calcd for $C_{19}H_{27}O_2$ $[M - CH_3]^+$ 287.2011, found 287.2022. Data for (*R*)-**8b** was identical.

*3-(6-(4-Methoxyphenyl)-3-methylhex-3-en-1-yl)-2,2-dimethyloxirane (**8c**).*[2a] Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)- or (*Z*)-**5a** (53 mg) and alkene **7c** (250 mg, containing 5% *p*-methoxytoluene) gave trisubstituted alkene **8c** (45 mg, 0.17 mmol, 66% from (*E*)-**5a**; 41 mg, 0.16 mmol, 60% from (*Z*)-**5a**) as a brown oil and a mixture of *E*/*Z* geometrical isomers [*E*/*Z* = 66:34 (from (*E*)-**5a**) or 67:33 (from (*Z*)-**5a**)]. 10.14469/hpc/5817. R_f 0.35 (5% EtOAc in petrol); ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6, 2H), 5.25 (br t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 2.72 - 2.66 (m, 1H), 2.63 – 2.54 (m, 2H), 2.34 – 2.23 (m, 2H), 2.21 – 2.04 (m, 2H), 1.70 (d, *J* = 1.3 Hz, *Z*-**8c**, 1H), 1.60 (s, *E*-**8c**, 2H), 1.66 – 1.46 (m, 2H), 1.30 (s, 3H), 1.26 (s, *E*-**8c**, 2H), 1.25 (s, *Z*-**8c**, 1H); The *E*:*Z* ratio was determined by integration of

the resonances at δ 1.60 (major) and 1.70 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 157.8, 134.9, 134.9, 134.5, 129.4, 125.3, 124.4, 113.8, 113.8, 64.3, 64.2, 58.4, 55.4, 36.4, 35.5, 35.2, 30.3, 30.2, 28.6, 27.6, 27.5, 25.0, 25.0, 23.5, 18.9, 18.8, 16.1. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.1 vs 23.5 ppm for the minor *Z*-isomer; HRMS (CI^+) *m/z* calcd for $C_{18}H_{27}O_2$ $[M + H]^+$ 275.2011, found 275.2008. Data for (*R*)-**8c** was identical.

*3-(6-(3-Methoxyphenyl)-3-methylhex-3-en-1-yl)-2,2-dimethyloxirane (**8d**).*[3d] Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)-**5a** (9.5 mg, 0.04 mmol, 1.0 equiv.) alkene **7d** (44 mg, 0.23 mmol, 5.0 equiv.), and ruthenium benzylidene **1** (3.4 mg, 0.004 mmol, 10 mol%) gave trisubstituted alkene **8d** (7.5 mg, 0.024 mmol, 61%) as a colourless oil and a mixture of *E*/*Z* geometrical isomers (*E*/*Z* = 72:28). 10.14469/hpc/6322. R_f 0.45 (10% EtOAc in pentanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.14 (m, 1H), 6.80 – 6.76 (m, 1H), 6.74 (d, *J* = 1.4 Hz, 1H), 6.75 – 6.70 (m, 1H), 5.31 – 5.12 (m, 1H), 3.80 (s, 3H), 2.72 – 2.66 (m, 1H), 2.65 – 2.59 (m, 2H), 2.37 – 2.27 (m, 2H), 2.22 – 2.03 (m, 2H), 1.70 (d, *J* = 1.3 Hz, 0.84H, *Z*-**8d**), 1.66 – 1.54 (m, 2H), 1.58 (d, *J* = 1.2 Hz, 2.16H, *E*-**8d**), 1.30 (s, 3H), 1.26 (s, 2.16H, *E*-**8d**), 1.25 (s, 0.84H, *Z*-**8d**). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.58 (major) and 1.70 (minor) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 159.7, 144.1, 135.0, 129.3, 125.2, 124.3, 121.0, 114.4, 111.1, 64.3, 64.2, 58.5, 55.3, 36.5, 36.2, 29.9, 28.7, 27.6, 25.0, 23.5, 18.9, 16.1. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.1 vs 23.5 ppm for the minor *Z*-isomer; HRMS (ES^+) calcd for $C_{18}H_{27}O_2$ $[M + H]^+$ 275.2011, found 275.2008.

*3-(6-(2-Methoxyphenyl)-3-methylhex-3-en-1-yl)-2,2-dimethyloxirane (**8e**).* Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)-**5a** (53 mg) and alkene **7e** (238 mg) gave trisubstituted alkene **8e** (54 mg, 0.20 mmol, 78%) as a light brown oil and a mixture of *E*/*Z* geometrical isomers (*E*/*Z* = 68:32). 10.14469/hpc/6323. R_f 0.15 (4% EtOAc in petrol); ^{1}H NMR (400 MHz $CDCl_3$) δ 7.20 – 6.81 (m, 4H), 5.30 – 5.22 (m, 1H), 3.83 (s, *E*-**8e**, 2.10H), 3.82 (s, *Z*-**8e**, 0.90H), 2.74 – 2.66 (m, 1H), 2.67 – 2.59 (m, 2H), 2.33 – 2.23 (m, 2H), 2.20 – 2.02 (m, 2H), 1.70 (d, *J* = 1.3 Hz, *Z*-**8e**, 0.90H), 1.69 – 1.44 (m, 2H), 1.58 (d, *J* =

1.3 Hz, *E*-**8e**, 2.10H), 1.30 (s, 3H), 1.26 (s, *E*-**8e**, 2.10H), 1.26 (s, *Z*-**8e**, 0.90H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.26 (major) and 1.26 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 157.5, 134.5, 130.6, 129.8, 127.0, 127.0, 125.7, 124.8, 120.3, 120.3, 110.2, 64.2, 64.2, 58.4, 55.2, 36.3, 30.8, 30.5, 28.5, 28.2, 27.5, 24.9, 23.4, 18.8, 18.7, 15.9. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 15.9 vs 23.4 ppm for the minor *Z*-isomer; HRMS (ES^+) *m/z* calcd for $C_{18}H_{27}O_2$ $[M + H]^+$ 275.2011, found 275.2007.

*2,2-Dimethyl-3-(3-methyl-6-(p-tolyl)hex-3-en-1-yl)oxirane (**8f**).*[2a] Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)-**5a** (53 mg) and alkene **7f** (218 mg) gave trisubstituted alkene **8f** (43 mg, 0.16 mmol, 65%) as a colourless oil and a mixture of *E*/*Z* geometrical isomers (*E*/*Z* = 72:28). 10.14469/hpc/6414. R_f 0.31 (10% EtOAc in pentanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 4H), 5.29 – 5.21 (m, 1H), 2.74 – 2.67 (m, 1H), 2.65 – 2.58 (m, 2H), 2.36 – 2.27 (m, 2H), 2.33 (s, 3H), 2.23 – 2.04 (m, 2H), 1.72 (d, *J* = 1.4 Hz, 0.84H, *Z*-**8f**), 1.72 – 1.51 (m, 2H), 1.62 (s, 2.16H, *E*-**8f**), 1.34 (s, 3H), 1.30 (s, 2.16H, *E*-**8f**), 1.29 (s, 0.84H, *Z*-**8f**). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.62 (major) and 1.72 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 139.3, 139.2, 135.2, 135.2, 134.8, 129.1, 129.0, 128.4, 125.3, 124.5, 64.2, 64.2, 58.4, 36.4, 35.9, 35.7, 30.2, 30.1, 28.6, 27.5, 27.5, 25.0, 25.0, 23.4, 21.1, 18.9, 18.8, 16.1. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.1 vs 23.4 ppm for the minor *Z*-isomer; HRMS (ES^+) calcd for $C_{18}H_{27}O$ $[M + H]^+$ 259.2062, found 259.2056.

*3-(6-(4-Chlorophenyl)-3-methylhex-3-en-1-yl)-2,2-dimethyloxirane (**8g**).* Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)-**5a** (53 mg) and alkene **7g** (244 mg) gave trisubstituted alkene **8g** (47 mg, 0.17 mmol, 68%) as a light brown oil and a mixture of *E*/*Z* geometrical isomers (*E*/*Z* = 78:22). 10.14469/hpc/6325. R_f 0.25 (4% EtOAc in petrol); ^{1}H NMR (400 MHz $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.12 – 7.08 (m, 2H), 5.22 – 5.15 (m, 1H), 2.71 – 2.64 (m, 1H), 2.64 – 2.56 (m, 2H), 2.34 – 2.23 (m, 2H), 2.21 – 2.01 (m, 2H), 1.69 (q, *J* = 1.3 Hz, *Z*-**8g**, 0.66H), 1.64 – 1.57 (m, 2H), 1.55 (s, *E*-**8g**, 2.34H), 1.29 (s, 3H), 1.26 (s, *E*-

8g, 2.34H), 1.25 (s, *Z*-**8g**, 0.66H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.26 (major) and 1.25 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 140.6, 135.3, 131.4, 129.8, 128.3, 128.3, 124.6, 123.8, 64.1, 58.3, 36.3, 35.6, 35.3, 29.7, 29.7, 28.5, 27.4, 27.3, 24.9, 23.3, 18.7, 16.0. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.0 vs 23.3 ppm for the minor *Z*-isomer; HRMS (CI^+) *m/z* calcd for $C_{17}H_{24}O^{35}Cl$ $[M + H]^+$ 279.1510, found 279.1510.

*2,2-Dimethyl-3-(3-methyldec-3-en-1-yl)oxirane (**8h**).* Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)-**5a** (53 mg) and alkene **7h** (175 mg) gave trisubstituted alkene **8h** (51 mg, 0.23 mmol, 92%) as a colourless oil and a mixture of *E*/*Z* geometrical isomers (*E*/*Z* = 70:30). 10.14469/hpc/5762. R_f 0.57 (10% Et_2O in pentanes); ^{1}H NMR (400 MHz, Acetone-*d6*) δ 5.24 – 5.14 (m, 1H), 2.64 (t, *J* = 6.3 Hz, *Z*-**8h**, 0.3H), 2.61 (t, *J* = 6.2 Hz, *E*-**8h**, 0.7H), 2.24 – 1.95 (m, 4H), 1.72 – 1.52 (m, 5H), 1.38 – 1.25 (m, 8H), 1.23 (s, *Z*-**8h**, 0.9H), 1.23 – 1.22 (m, 3H), 1.21 (s, *E*-**8h**, 2.1H), 0.92 – 0.85 (m, 3H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.21 (major) and 1.23 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-*d6*) δ 133.8, 125.6, 124.7, 62.8, 62.7, 57.6, 57.5, 35.9, 31.2, 29.5, 29.3, 28.4, 28.3, 28.0, 27.3, 27.2, 26.9, 24.6, 24.6, 23.1, 22.1, 18.5, 18.5, 15.7, 13.9. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 15.7 vs 23.1 ppm for the minor *Z*-isomer; HRMS (CI^+) *m/z* calcd for $C_{15}H_{29}O$ $[M + H]^+$ 225.2213, found 225.2212.

*8-(3,3-Dimethyloxiran-2-yl)-6-methyloct-5-en-2-one (**8i**).*[42] Following the general procedure for relay cross metathesis using epoxy allyl ether (*E*)-**5a** (53 mg) and alkene **7l** (0.18 mL) gave trisubstituted alkene **8i** (34 mg, 0.16 mmol, 64%) as a light brown oil and a mixture of *E*/*Z* geometrical isomers (*E*/*Z* = 73:27). 10.14469/hpc/5764. R_f 0.21 (20% Et_2O in pentanes); IR (ATR, neat) 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 – 5.07 (m, 1H), 2.69 (t, *J* = 6.3 Hz, *Z*-**8i**, 0.27H), 2.65 (t, *J* = 6.3 Hz, *E*-**8i**, 0.73H), 2.47 – 2.41 (m, 2H), 2.29 – 2.21 (m, 2H), 2.12 (s, 3H), 2.19 – 2.00 (m, 2H), 1.68 – 1.56 (m, 5H), 1.29 (s, *Z*-**8i**, 0.81H), 1.28 (s, *E*-**8i**, 2.19H), 1.25 (s, *Z*-**8i**, 0.81H), 1.24 (s, *E*-**8i**, 2.19H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.24 (major) and 1.25 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 208.8, 135.6, 135.6,

124.2, 123.3, 64.2, 64.2, 58.4, 43.9, 43.8, 36.4, 30.1, 30.1, 28.6, 27.5, 27.5, 25.0, 25.0, 23.4, 22.5, 22.3, 18.9, 18.9, 16.1. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.1 vs 23.4 ppm for the minor *Z*-isomer; HRMS (ES^+) *m/z* calcd for $C_{13}H_{23}O_2$ $[M + H]^+$ 211.1693, found 211.1693.

*(S)-2,6-Dimethylhept-6-ene-2,3-diol (**5i**).*[43] Following the general procedure for relay cross metathesis using diol (*S*)-**5b** (57 mg) and alkene **7a** (200 mg) gave truncated alkene **5i** (10 mg, 0.06 mmol, 24%) as an inseparable 85:15 mixture containing (*S*,6*E*)-2,6-dimethyl-8-(prop-1-en-1-yloxy)oct-6-ene-2,3-diol (**10b**) (*E*/*Z* = 2:1). Vinyl ether **10b** was identified by comparison of spectroscopic data with epoxide analogue **10a**, and the *E/Z* ratio was determined by ^{1}H NMR and assigned on the basis of characteristic $^3J_{H\text{-}H}$ coupling constants. 10.14469/hpc/5765. R_f 0.40 (40% EtOAc in petrol); IR (ATR, neat) 3600-3100, 3075, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (dq, *J* = 12.6, 1.6 Hz, 0.1H, *E*-**10b**), 5.96 (dq, *J* = 6.2, 1.6 Hz, 0.05H, *Z*-**10b**), 5.42 (tq, *J* = 6.7, 1.3 Hz, 0.15H, **10b**), 4.84 – 4.76 (m, 0.1H, **10b**), 4.74 (s, 0.85H), 4.73 (s 0.85H), 4.44 – 4.35 (m, 0.05H, *Z*-**10b**), 4.26 (d, *J* = 6.7 Hz, 0.1H, *Z*-**10b**), 4.18 (d, *J* = 6.7 Hz, 0.2H, *E*-**10b**), 3.36 (d, *J* = 10.6 Hz, 0.85H), 3.34 (d, *J* = 11.9 Hz, 0.15H, **10b**), 2.38-2.20 (m, 2H), 2.16 – 2.01 (m, 2H), 1.74 (d, *J* = 1.2 Hz, 2.6H), 1.69 (d, *J* = 1.4 Hz, 0.5H, **10b**), 1.67 – 1.53 (m, 1.5H), 1.50 – 1.39 (m, 1H), 1.21 (s, 2.5H), 1.20 (s, 0.5H, **10b**), 1.16 (s, 2.5H), 1.15 (s, 0.5H, **10b**). For **5i** only: ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.9, 110.5, 79.4, 72.7, 35.0, 29.6, 26.6, 23.4, 22.6; HRMS (ES^+) *m/z* calcd for $C_9H_{17}O$ $[M - OH]^+$ 141.1279, found 141.1283.

*(S)- and (R)-4,4-Dimethyl-5-(3-methyl-6-phenylhex-3-en-1-yl)-2-phenyl-1,3,2-dioxaborolane [(S)-**8j** and (R)-**8j**]*. Following the general procedure for relay cross metathesis using boronates (*S*)- or (*R*)-**5g** (59 mg, 0.19 mmol, 1.0 equiv.), alkene **7a** (150 mg, 0.94 mmol, 5.0 equiv.), and ruthenium benzylidene **1** (16 mg, 0.019 mmol, 10 mol%) gave trisubstituted alkenes (*S*)-**8j** (38 mg, 0.11 mmol, 58%) or (*R*)-**8j** (44 mg, 0.13 mmol, 68%) as brown oils and a mixture of *E*/*Z* geometrical isomers [(*S*)-**8j**: *E/Z* = 60:40; (*R*)-**8j**: *E/Z* = 62:38]. 10.14469/hpc/6328. R_f 0.40 (5% EtOAc in petroleum ether, streaking); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 2H), 7.50 – 7.32 (m, 3H), 7.30 – 7.14 (m, 5H), 5.32 – 5.23 (m, 1H), 4.03 (dd, *J* = 10.0, 3.5 Hz, *E*-**8j**,

0.60H), 3.98 (dd, *J* = 10.4, 3.2 Hz, *Z*-**8j**, 0.40H), 2.69 – 2.62 (m, 2H), 2.44 – 2.06 (m, 4H), 1.72 (d, *J* = 1.3 Hz, *Z*-**8j**, 1.20H), 1.74 – 1.63 (m, 1H), 1.59 (s, *E*-**8j**, 1.80H), 1.62 – 1.47 (m, 1H), 1.42 (s, *E*-**8j**, 1.80H), 1.41 (s, *Z*-**8j**, 1.20H), 1.28 (s, *E*-**8j**, 1.80H), 1.25 (s, *Z*-**8j**, 1.20H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.28 (major) and 1.25 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 142.3, 135.1, 135.0, 134.8, 131.3, 128.5, 128.5, 128.2, 127.7, 125.7, 125.4, 124.2, 85.2, 85.1, 82.1, 82.0, 36.4, 36.1, 30.1, 30.0, 29.8, 28.8, 28.7, 28.6, 23.5, 23.4, 23.3, 16.1. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.1 vs 23.3 ppm for the minor *Z*-isomer; HRMS (CI^+) *m/z* calcd for $C_{23}H_{30}{}^{11}BO_2$ $[M + H]^+$ 349.2333, found 349.2332.

*(S)- and (R)-6-Methyl-8-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)oct-5-en-2-one [(S)-**8k** and (R)-**8k**]*.[39] Following the general procedure for relay cross metathesis using acetonide (*S*)- or (*R*)-**5d** (67 mg) and alkene **7l** (158 mg) gave trisubstituted alkenes (*S*)-**8k** (46 mg, 0.17 mmol, 69%) or (*R*)-**8k** (42 mg, 0.16 mmol, 62%) as colourless oils and a mixture of *E/Z* geometrical isomers [(*S*)-**8k**: *E/Z* = 73:27; (*R*)-**8k**: *E/Z* = 70:30]. 10.14469/hpc/5767. R_f 0.24 (10% EtOAc in petrol); IR (ATR, neat) 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 – 5.07 (m, 1H), 3.61 (dd, *J* = 9.4, 3.4 Hz, 1H), 2.48 – 2.38 (m, 2H), 2.30 – 2.10 (m, 3H), 2.11 (s, 3H), 2.04 – 1.93 (m, 1H), 1.69 – 1.64 (m, *Z*-**8k**, 0.81H), 1.61 (s, *E*-**8k**, 2.19H), 1.60 – 1.51 (m, 1H), 1.48 – 1.40 (m, 1H), 1.39 (d, *J* = 0.8 Hz, 3H), 1.31 – 1.28 (m, 3H), 1.23 – 1.20 (m, 3H), 1.06 (s, 3H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.61 (major) and 1.69 – 1.64 (minor) ppm; $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 208.6, 135.7, 124.1, 123.0, 121.3, 106.5, 106.4, 82.8, 82.6, 80.1, 43.9, 43.7, 36.6, 29.9, 28.9, 28.6, 28.6, 27.6, 27.5, 26.8, 26.0, 26.0, 23.2, 22.9, 22.4, 22.2, 16.0. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.0 vs 23.2 ppm for the minor *Z*-isomer; HRMS (EI^+) calcd for $C_{16}H_{28}O_3$ $[M]^{\bullet+}$ 268.2038, found 268.2045.

*(S)- and (R)-8-(5,5-Dimethyl-2-phenyl-1,3,2-dioxaborolan-4-yl)-6-methyloct-5-en-2-one [(S)-**8l** and (R)-**8l**]*. Following the general procedure for relay cross metathesis using boronates (*S*)- or (*R*)-**5g** (59 mg, 0.19 mmol, 1.0 equiv.), alkene **7l** (118 mg, 0.94 mmol, 5.0 equiv.), and ruthenium benzylidene **1** (16 mg, 10 mol%)

gave trisubstituted alkenes (*S*)-**8l** (32 mg, 0.10 mmol, 55%) or (*R*)-**8l** (35 mg, 0.11 mmol, 60%) as brown oils and a mixture of *E*/*Z* geometrical isomers ((*S*)-**8l**: *E*/*Z* = 74:26; (*R*)-**8l**: *E*/*Z* = 76:24). 10.14469/hpc/6329. R_f 0.10 (10% EtOAc in petrol); IR (ATR, neat) 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.79 (m, 2H), 7.49 – 7.43 (m, 1H), 7.40 – 7.34 (m, 2H), 5.17 (m, 1H), 4.04 (dd, *J* = 10.0, 3.4 Hz, *E*-**8l**, 0.76H), 4.03 (dd, *J* = 10.0, 3.4 Hz, *Z*-**8l**, 0.24H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.38 – 2.26 (m, 3H), 2.16 – 2.05 (m, 1H), 2.14 (s, *E*-**8l**, 2.28H), 2.11 (s, *Z*-**8l**, 0.72H), 1.80 – 1.52 (m, 2H), 1.71 (d, *J* = 1.3 Hz, *Z*-**8l**, 0.72H), 1.67 (d, *J* = 1.3 Hz, *E*-**8l**, 2.28H), 1.44 (s, *Z*-**8l**, 0.72H), 1.43 (s, *E*-**8l**, 2.28H), 1.28 (s, 3H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.67 (major) and 1.71 (minor) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 208.8, 208.7, 135.7, 135.6, 134.8, 131.3, 131.3, 127.8, 127.7, 124.3, 123.1, 85.3, 85.1, 82.1, 82.1, 43.9, 43.7, 36.4, 30.1, 30.0, 29.9, 29.8, 28.8, 28.5, 23.4, 23.4, 23.3, 22.4, 22.3, 16.1. The E-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance[23] at 16.1 vs 23.3 ppm for the minor *Z*-isomer; HRMS (CI^+) calcd for $C_{19}H_{28}{}^{11}BO_3$ $[M + H]^+$ 315.2126, found 315.2117.

(2R,4aR,10aS)-6-Methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol ***(11)***.[2a] To a solution of epoxy alkene *(R)*-**8c** (50 mg, 0.18 mmol, 1.0 equiv.) in CH_2Cl_2 (1.8 mL) at -78 °C was added dropwise boron trifluoride diethyl etherate (44 μL, 0.36 mmol, 2.0 equiv.) and the reaction mixture was stirred at -78 °C for 1 h before allowing to warm to room temperature. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried (Na_2SO_4), evaporated and chromatographed (10-15% EtOAc in petrol) to give tricycle **11** (18.2 mg, 0.066 mmol, 56% from (*R*,*E*)-**8c**) as a colourless viscous oil. 10.14469/hpc/6333. R_f 0.33 (20% EtOAc in petrol); $[a]_D^{26}$ +34.2 (*c* 1.0, $CHCl_3$); IR (ATR, neat) 3600-3200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.77 (s, 3H), 3.38 – 3.25 (m, 1H), 2.91 (ddd, *J* = 16.8, 6.6, 1.5 Hz, 1H), 2.79 (ddd, *J* = 16.8, 11.8, 7.1 Hz, 1H), 2.27 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.93 – 1.68 (m, 4H), 1.57 (dd, *J* = 13.0, 4.7 Hz, 1H), 1.38 (d, *J* = 5.8 Hz, 1H), 1.32 (dd, *J* = 12.2, 2.4 Hz, 1H), 1.20 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.7, 150.6, 129.8, 127.3, 111.0, 110.2, 78.7, 55.3, 49.8,

39.0, 37.8, 36.9, 29.8, 28.2, 28.0, 24.8, 18.9, 15.4; HRMS (ES^+) calcd for $C_{18}H_{27}O_2$ $[M + H]^+$ 275.2011, found 275.2018.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^1H and ^{13}C NMR spectra for all compounds; HPLC chromatograms for enantiomeric excess determinations of (*S*)- and (*R*)-**5c** and (*S*)- and (*R*)-**5g**.

Corresponding Author

*E-mail: c.braddock@imperial.ac.uk

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23. The *E*:*Z* ratio of trisubstituted alkenes was determined by ^{1}H NMR integration of selected signals (see experimental section). The *E* isomers were identified as the major isomers on the basis of their characteristically shielded methyl groups of the trisubstituted olefin in the ^{13}C NMR spectrum. See *e.g.*, for *E*- and *Z*-**8i**: Watanabe, Y.; Laschat, S; Budde, M.; Affolter, O.; Shimada, Y.; Urlachera, V. B. Oxidation of acyclic monoterpenes by P450 BM-3 monooxygenase: influence of the substrate *E*/*Z*-isomerism on enzyme chemo- and regioselectivity. *Tetrahedron* **2007**, *63*, 9413–9422.

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28. Tricycle **10** has previously only been reported as a racemate (see *e.g.*, ref 2a).

29. ^{1}H NMR, ^{13}C NMR, IR and MS data are available via a data repository as: Bahou, K. A.; D. C. Braddock, D. C; Z. Shi, Z.; He, T. Imperial College HPC Data Repository, **2019**. DOI: 10.14469/hpc/5737 (accessed 16/09/2019).

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