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Asymmetric dihydroxylation of vinyl sulfones: routes to enantioenriched α-hydroxyaldehydes and the enantioselective syntheses of furan-2(5*H*)-ones

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Abstract—The asymmetric dihydroxylation of α,β-unsaturated sulfones under Sharpless conditions affords enantioenriched α-hydroxyaldehydes in a complex mixture of dimeric species. These mixtures undergo olefination generating the corresponding α,β-unsaturated esters or furan-2(5*H*)-ones with high levels of enantiomeric excess. The application of this method for the rapid stereoselective synthesis of the furanone natural products; quercus lactone and maritolide, are described.

1. Introduction

Asymmetric dihydroxylation, pioneered by Sharpless has emerged as a most reliable method for the generation of asymmetry from a prochiral alkene.[1] This remarkable reaction proceeds efficiently with both electron rich and electron poor alkenes.[1,2] Somewhat surprisingly this asymmetric transformation has never been reported using readily available α,β-unsaturated (vinyl) sulfones **1** as substrates (see Fig. 1, where X=SO_2R').[3] We envisaged that this reaction would provide an efficient route towards a one-step procedure for the preparation of synthetically useful optically enriched α-hydroxyl carbonyl molecules, of the type **3**,[4] via the 1,2-elimination of the intermediate α-hydroxyl sulfone **2**.[5]

Similar examples employing different vinyl substituents have been reported previously, in both racemic and asymmetric senses. The dihydroxylation and subsequent rearrangement of vinyl chlorides, bromides (where X=Cl, Br)[6] and enol ethers (where X=OR′),[7,8] generating non-enolisable α-hydroxyaldehydes **3a** and ketones have all been performed in an asymmetric manner under both reagent and substrate control. More recently it has been reported that α,β-unsaturated nitriles[9a] and phosphonates[9] undergo racemic dihydroxylation. Affording, in these instances, the corresponding base labile cyanohydrins and phosphates **2** (where X=CN and $PO(OR')_2$, respectively).

In relation to the proposed sulfonyl sequence, examples demonstrate that in situ generated α-alkoxy sulfones undergo a facile, spontaneous 1,2-elimination reaction, affording the corresponding aldehyde, or ketone and sulfinate anion. The most frequently used exemplification of this type of transformation is the oxidation-elimination of sulfonyl carbanions.[10] An additional series of examples, indicate that α,β-epoxy sulfones undergo ring opening in the β-position by a suitable nucleophilic species (e.g. Br^-, etc.), and that the resultant oxide eliminates the sulfonyl moiety thereby generating an aldehyde.[11] This method has subsequently been employed in an iterative sense for the synthesis of poly-*trans*-fused tetrahydropyrans.[12] Additionally, it is widely reported that the products of Pummerer rearrangements collapse in a similar manner following their basic hydrolysis (X=SR′).[13]

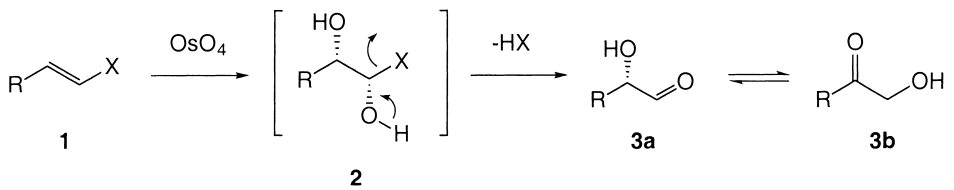

Figure 1. Asymmetric hydroxylation—1,2-hydroxyl elimination. Where X=Cl, Br, OR′, SR′, SO_2R', NO_2, CN, $PO(OR')_2$, etc.; R′=alkyl, aryl, etc.

Keywords: asymmetric dihydroxylation; vinyl sulfones; prochiral alkene; α-hydroxyaldehydes.
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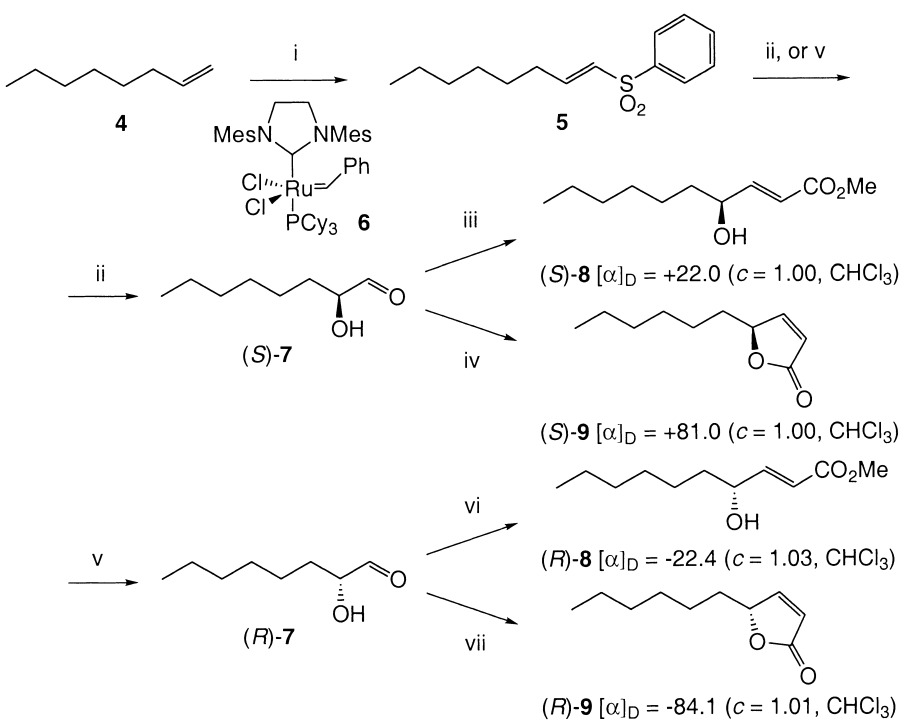
2. Results and discussion

At the outset a potential problem with the proposed sequence was that the enantioenriched α-hydroxyaldehyde **3a** may undergo enolisation into the corresponding ketone **3b** with the concomitant erosion of optical activity (Fig. 1). For this reason unprotected hydroxyl species such as **3a** have traditionally found limited use in organic synthesis.[4] Nevertheless, in order to investigate the proposed reaction sequence β-substituted phenyl vinyl sulfone **5** was synthesised following a ruthenium catalysed cross metathesis reaction. Thus, under conditions described,[14] octene **4** and phenyl vinyl sulfone were heated in the presence of 5 mol% of the imidazoyl catalyst **6** affording the corresponding *trans*-vinyl sulfone **5** in excellent yield. Treatment of sulfone **5** with either AD mix-α, or AD mix-β, under standard conditions, resulted in consumption of the starting material and observation of a slower moving 'streaking' spot on thin layer chromatography. The identity of these compounds appeared, by ^{1}H NMR spectroscopy, to be a complex mixture containing the α-hydroxyaldehyde (*S*/*R*)-**7** and unidentified materials, likely to include the corresponding homo-dimer (see Scheme 2). Rather than attempting to purify these materials by flash column chromatography, it was found that direct conversion into the corresponding α,β-unsaturated ester using a Horner–Wadsworth–Emmons (H–W–E) protocol gave improved yields of characterisable materials (Scheme 1). Thus, AD mix-α ultimately afforded ester (*S*)-**8** in 52% yield for the 2 steps, whereas AD mix-β gave enantiomeric (*R*)-**8** in 49% yield (Scheme 1).[15] Concerns regarding the stereochemical integrity of the α-hydroxyl group during these operations proved to be unfounded and the optical rotation measurements obtained for both products compare favourably with the literature value measured for (*R*)-**8** {$[\alpha]_D^{23}=-20.2$ (c=1.0, $CHCl_3$), 93% e.e}.[15] More significantly analytical HPLC of (*R*)- and (*S*)-**8**, using a Whelk stationary phase, indicated that the enantiomeric excesses of (*S*)-**8** and (*R*)-**8**, following either reaction, were both approximately 90% e.e. Due to slight peak overlap the calculation of more accurate enantiomeric excess values was not possible.

We were interested to apply this novel method to the synthesis of optically active 5-alkyl substituted furan-2(5*H*)-ones (γ-butenolides) using the *cis*-selective Still–Gennari modified Horner–Wadsworth–Emmons reaction.[16–18] The furan-2(5*H*)-one sub-structure appears in a very large number of natural products; including those from diverse species such as marine animals and plants.[18] Furthermore, many such compounds possess interesting biological activities, indeed in the case of the acetogenin family[19] it has been shown that the furan-2(5*H*)-one functional group is responsible for their potent cytotoxity.

Thus, treatment of the crude (*S*)-**7** under modified Still–Genari conditions[20] afforded a mixture of the ester (*S*)-**8** and the furan-2(5*H*)-one (*S*)-**9** in approximately a 40:60 ratio (^{1}H NMR spectroscopy), evidently resulting from only a moderately *cis* selective H–W–E reaction. Separation by flash column chromatography gave the lactone (*S*)-**9** in 26% yield and the ester (*S*)-**8** in 19% yield. Similarly, the enantiomeric series was accessed using AD mix-β in comparable yield (Scheme 1). The optical rotation measurements were approximately equal and opposite and analytical chiral HPLC using a Whelk column indicated enantiomeric excesses of 88 and 95% for (*S*)- and (*R*)-**9**, respectively.



Scheme 1. (i) Phenyl vinyl sulfone, **6** (5 mol%), DCM (1.0 mol dm^{-3}), 40°C, 15 h, 90%; (ii) AD-mix-α, $MeSO_2NH_2$, $^tBuOH–H_2O$ (1:1), 25°C, 24 h; (iii) $(EtO)_2POCH_2CO_2Me$, NaH, THF, 20°C, 12 h, 52% (yield from **5**); (iv) $(F_3CCH_2O)_2POCH_2CO_2Me$, NaH, THF, −78°C to 20°C, 5 h, 26% (yield from **5**); (v) AD-mix-β, $MeSO_2NH_2$, $^tBuOH–H_2O$ (1:1), 25°C, 24 h; (vi) $(EtO)_2POCH_2CO_2Me$, NaH, THF, 20°C, 12 h, 49% (yield from **5**); (vii) $(F_3CCH_2O)_2POCH_2Me$, NaH, THF, −78°C to 20°C, 12 h, 23% (yield from **5**).

Attempts to further optimise this two-step process were not successful and it appears that the mass balance for this reaction exists as polar unidentified materials. Additionally, it seems possible that some of the intermediate aldehyde is lost in the aqueous phase as the corresponding hydrate **16** (see Scheme 2).

The overall stereochemical outcome for these reactions, based on the literature precedent for enantioenriched (*R*)-**8**,[15] is consistent with the Sharpless mnemonic[1] in which the phenyl sulfonyl moiety represents the largest group (see Fig. 2).

Based on the excellent enantioselectivity observed it appears that the equilibrium between the α-hydroxyaldehyde **3a** and the α-hydroxyketone **3b**, via enol **15** (Scheme 2), and the resultant erosion of enantiopurity, is not significant in this case.[4d] A possible explanation for this is that in organic solvents the reactive monomeric aldehyde **3a** dimerises forming the corresponding bis-hemiacetals **10** and **11**, as a complex mixture of diastereoisomers.[13,21] Mass spectroscopy (ES) demonstrates the existence of this type of dimeric compound where R=^{n}Hex. Consequently it seems plausible that these species serve to effectively 'protect' the potentially labile asymmetric centre and that subsequent reaction of **10**, **11** or **3a** under Horner–Wadsworth–Emmons conditions generates the corresponding enantioenriched α,β-unsaturated esters. Similarly, in aqueous conditions it has been shown that α-hydroxyaldehydes undergo significant hydration (**3a→16**)[4d] again protecting the asymmetric carbon from epimerisation.

Attempts to unambiguously characterise the crude reaction mixture, following treatment of the vinyl sulfone **5** with AD mix-β (where R=^{n}Hex), by PDC oxidation afforded a mixture of compounds from which only the unusual acetal **13** was isolated, as a single undetermined diastereoisomer in 12% yield. Notably throughout this study none of the products resulting from the H–W–E reaction of the α-hydroxyketone **3b**, the ketone itself, or its dimer **14**, were detected.

In order to further exemplify and explore this process as a rapid method for the construction of enantioenriched furan-2(5*H*)-ones a short synthesis of the natural product **21**,

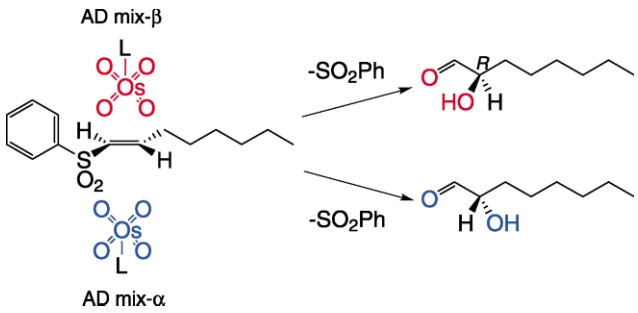
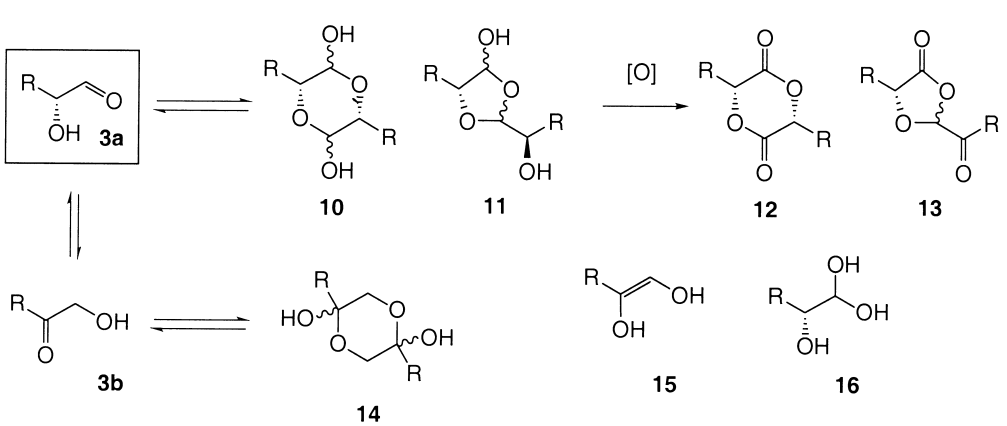


Figure 2. Sharpless model for asymmetric dihydroxylation—AD mix-β [L=$(DHQD)_2PHAL$]; AD mix-α [L=$(DHQ)_2PHAL$].

called variously quercus (isolated from a species of white oak), whisky and cognac lactone depending on its origin,[22] was performed. Vinyl sulfone **17** was prepared following cross metathesis as described above. On treatment, initially with AD-mix-β, then with the bis-trifluoroethanol derived phosphonate anion, **17** was converted into the corresponding furan-2(5*H*)-one **20** {$[\alpha]_D^{20}=-103.0$ (c=1.05, $CHCl_3$)} and the ester **19** {$[\alpha]_D^{20}=-21.0$ (c=1.0, $CHCl_3$)} in 34 and 19% isolated yields, respectively.[23] Stereoselective conjugate addition using Me_2CuLi afforded the lactone **21**, whose data was entirely consistent with that previously reported (Fig. 3).[22,23] This sequence again providing corroboration for the predictive approach of the putative OsO_4-L complex presented in Figure 2.

In a similar manner a short synthesis of both enantiomers of maritolide **26** was approached. This relatively simple 5-alkyl furan-2(5*H*)-one was isolated in 1998 from the shrub *diospyros maritima* a member of the ebony family (*ebenaceae*) in Taiwan.[24] Historically the stems of this shrub have been used to treat rheumatic diseases in this region. Maritolide **26** has not previously been prepared synthetically and the absolute stereochemistry of the single asymmetric carbon is not known.

Initially dec-9-en-1-ol **22** was oxidised using PDC to the carboxylic acid **23**, which was then esterified, under standard Fischer type conditions, affording the ethyl ester **24** in 64% yield for the 2 steps. At this stage both the cross metathesis catalytic loading and the catalyst itself were



Scheme 2.

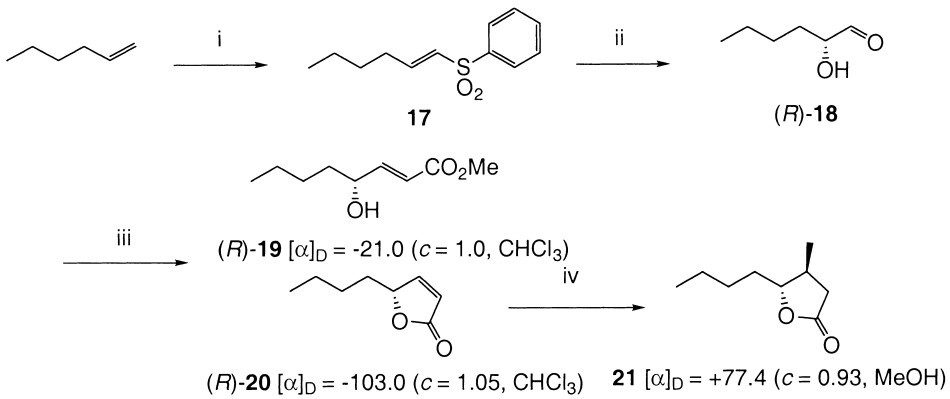


Figure 3. Synthesis of quercus lactone **21**. (i) Phenyl vinyl sulfone, **6** (5 mol%), DCM, 40°C, 12 h, 86%; (ii) AD-mix-β, ^{t}BuOH–H_2O (1:1), 15°C, 24 h; (iii) $(F_3CH_2CO)_2POCH_2CO_2Me$, NaH, THF, −78°C to rt, 24 h, 34% (yield from **17**); (iv) Me_2CuLi, Et_2O, −78°C to −20°C, 1 h, 67%.

investigated in an attempt to prepare sulfone **25** in the most efficient sequence. It was found that use of the biscyclohexylphosphine Grubbs' catalyst gave only the dimer resulting from cross metathesis of **24** and recovered phenyl vinyl sulfone.[14] Use of 1 mol% of **6** afforded the vinyl sulfone **25** in 44% yield, however, the remaining phenyl vinyl sulfone proved difficult to separate. The corresponding process using 5 mol% of **6** gave **25** in 89% yield following essentially a complete cross metathesis reaction (Fig. 4).

Treatment of **25** with either AD mix-α, or β gave the intermediate aldehydes that were directly converted into the corresponding (*R*)- and (*S*)-furanones **26** in 28 and 22% yields, respectively. The corresponding (*R*)- and (*S*)-4-hydroxyl esters **27** were also obtained following these reactions in 13% yield in both instances. The spectroscopic data obtained for **26** was entirely consistent with that reported.[24] However, the roughly equal and opposite optical rotation values obtained for (*R*)- and (*S*)-**26** differed greatly from the literature value $\{[\alpha]_D^{24}=-3.4$ (c=0.2, $CHCl_3$)$\}$,[24] consequently we speculate that **26** underwent racemisation during the isolation process, or is formed biosynthetically without stereocontrol. Chiral HPLC data obtained for both (*R*)-**26** and (*S*)-**26** indicate enantiomeric excesses of approximately 96 and 95%, respectively (Chiralpak AD). Similarly, as expected chiral HPLC analysis of (*R*)- and (*S*)-**27** indicated approximately identical enantiomeric ratios to their furan-2(5*H*)-one counterparts (Whelk).

3. Conclusion

To summarise, we have developed a novel method for the synthesis of enantioenriched furan-2(5*H*)-ones and 4-hydroxyl α,β-unsaturated esters from the corresponding vinyl sulfones. The main advantages of the sequence described stem from the rapid access of functionalised products in high enantiomeric purity and in a

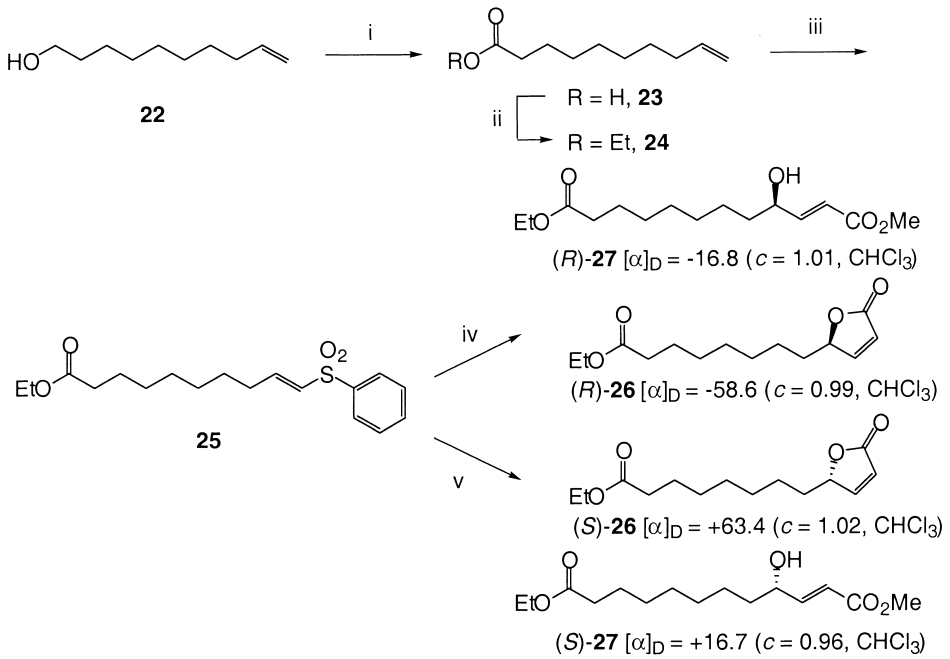
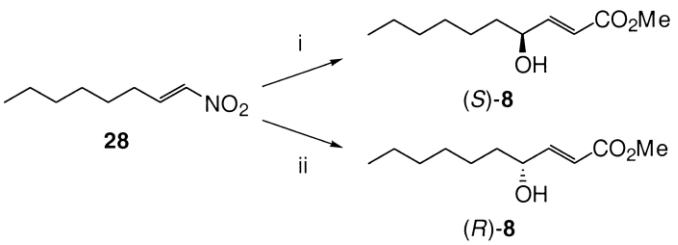


Figure 4. Synthesis of (*R*)-maritolide and (*S*)-maritolide **26**. (i) PDC, DMF, rt, 69%; (ii) cat. H_2SO_4, EtOH, 80°C, 93%; (iii) phenyl vinyl sulfone, **6** (5 mol%), DCM, 40°C, 89%; (iv) (a) AD mix-β, ^{t}BuOH–H_2O (1:1), 10°C; (b) $(F_3CH_2CO)_2POCH_2CO_2Me$, NaH, THF, −78°C to rt, 28% (from **25**); (v) (a) AD mix-α, ^{t}BuOH–H_2O (1:1), 10°C; (b) $(F_3CH_2CO)_2POCH_2Me$, NaH, THF, −78°C to rt, 22% (from **25**).



Scheme 3. (i) (a) AD-mix-α, $MeSO_2NH_2$, $^tBuOH–H_2O$ (1:1), 20°C, 24 h; (b) $(EtO)_2POCH_2CO_2Me$, NaH, THF, 25°C, 4 h, 20% (yield from **28**); (ii) (a) AD-mix-β, $MeSO_2NH_2$, $^tBuOH–H_2O$ (1:1), 20°C, 24 h; (b) $(EtO)_2POCH_2CO_2Me$, NaH, THF, 25°C, 12 h, 26% (yield from **28**).

stereochemically predictable manner from readily available vinyl sulfone starting materials. Preliminary results indicate that this process may be more general than described in this paper, for example, α,β-unsaturated nitro compound **28**[25] gave (*S*)- and (*R*)-**8** under identical conditions to those described (Scheme 3). Interestingly, the same overall stereoselectivity was observed for the nitro variant as the sulfonyl version, i.e. AD mix-α gave (*S*)-**8**, whereas AD mix-β gave (*R*)-**8** in approximately 90% e.e. for both cases. However, the chemical yields observed were considerably worse than those for the corresponding vinyl sulfone **5**, partly due to the competing hydrolysis/*retro* nitro-aldol reaction of **28** under the asymmetric dihydroxylation reaction conditions.

Future work will focus both on improving the yields and to further explore the substrate scope and limitations of the 1,2-elimination process described. Initial results indicate that the asymmetric α-hydroxyl substituent is responsible for the poor geometrical stereoselectivity of the Still–Gennari olefination; under identical conditions to those described aliphatic straight chain aldehydes gave the expected, reported stereoselectivities (*E*/*Z*, 15:85) for this H–W–E reagent.[16,20]

4. Experimental

4.1. General

Starting materials were purchased from commercial sources and were used without further purification. Anhydrous THF was distilled under nitrogen from the sodium-benzophenone ketyl radical, DCM was distilled from CaH_2. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. Infrared spectroscopy was performed on a Perkin–Elmer Paragon 1000 FTIR spectrometer. Optical rotation measurements were recorded using a Optical Activity, Polaar 2001 polarimeter at 589 nm and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography, under moderate pressure was performed using silica gel—ICN 32-63, 60 Å. Analytical HPLC measurements were performed on a Gilson analytical HPLC machine using either a (*R*,*R*)-Whelk column (Merck), or a Chiralpak AD column (Daicel) under conditions described in Section 4.

4.1.1. [(*trans*-Oct-1-ene)-1-sulfonyl]benzene 5.[26] Under N_2, a solution of 1-octene (2.0 cm^3, 12.7 mmol, 1.5 equiv.), phenyl vinyl sulfone (1.41 g, 8.38 mmol, 1 equiv.) and **6** (356 mg, 0.42 mmol, 5 mol%) in DCM (10 cm^3) was heated to reflux for 12 h. Silica (ca. 5 g) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography (Hex–EtOAc; 4:1) gave the vinyl sulfone **5** (1.89 g, 90%) as a pale yellow oil. R_f=0.3 (Hex–EtOAc; 4:1); ν_{max} (neat/cm^{-1}) 3035, 2927, 2856, 1624, 1446, 1305, 1147; *m*/*z* (CI) 270 (MNH_4^+, 100%); found 270.15350, $C_{14}H_{20}O_2S{\cdot}NH_4$ requires 270.15280 (+2.9 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.0 Hz, CH_3), 1.23–1.37 (6H, m, CH_2), 1.48 (2H, pent, *J*=7.0 Hz, CH_2), 2.23 (2H, dq, *J*=7.0 Hz, CH_2), 6.31 (1H, dt, *J*=1.5, 15.0 Hz, CH), 7.00 (1H, dt, *J*=7.0, 15.0 Hz, CH), 7.54 (2H, t, *J*=7.0 Hz, ArH), 7.62 (1H, t, *J*=7.0 Hz, ArH), 7.89 (2H, d, *J*=7.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 13.9, 22.4, 27.5, 28.7, 31.4, 31.5, 127.5, 129.2, 130.4, 133.1, 140.9, 147.3.

4.1.2. *trans*-4*R*-Hydroxydec-2-enoic acid methyl ester 8. A solution of the vinyl sulfone (485 mg, 1.92 mmol, 1 equiv.) in ^tBuOH (8 cm^3) and H_2O (8 cm^3) was treated with $MeSO_2NH_2$ (229 mg, 2.41 mmol, 1.25 equiv.) and AD mix-β (7.7 g) for 24 h. DCM (25 cm^3) and H_2O (25 cm^3) were added and the mixture was partitioned for 0.5 h. The resultant aqueous layer was further extracted with DCM (4×25 cm^3) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude aldehyde. Under N_2, at room temperature a solution of methyl diethylphosphonoacetate (445 mg, 2.12 mmol, 1.1 equiv.) in dry THF (20 cm^3) was treated with 60% (w/w) NaH in mineral oil (77 mg, 1.93 mmol, 1 equiv.) for 0.5 h. The crude aldehyde in THF (5 cm^3) was added and the reaction was stirred for 15 h. Et_2O (25 cm^3) and H_2O (25 cm^3) were added and the resultant aqueous layer was further extracted with Et_2O (3×25 cm^3). The combined extracts were dried over $MgSO_4$ before filtration and solvent removal and purification by flash column chromatography (Hex–EtOAc; 4:1) gave (*R*)-**8** (188 mg, 49%) as a clear liquid. R_f=0.2 (Hex–EtOAc; 4:1); $[\alpha]_D^{20}$=−22.4 (*c*=1.03, $CHCl_3$) {lit. $[\alpha]_D^{23}$=−20.2 (*c*=1.0, $CHCl_3$), 93% e.e.};[15] ν_{max} (neat/cm^{-1}) 3432, 2930, 2857, 1726, 1659, 1435, 1277, 1169; *m*/*z* (CI) 218 (MNH_4^+, 100%), 201 (MH^+, 50%); found 201.14956, $C_{11}H_{21}O_3{\cdot}H$ requires 201.14906 (+2.8 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.0 Hz, CH_3), 1.22–1.46 (8H, m, CH_2), 1.54–1.63 (2H, m, CH_2), 2.02 (1H, s(br), OH), 3.74 (3H, s, CH_3), 4.25–4.33 (1H, m(br), CH), 6.02 (1H, dd, *J*=1.5, 15.5 Hz, CH), 6.94 (1H, dd, *J*=5.0, 15.5 Hz, CH); δ_C (100 MHz, $CDCl_3$) 14.0, 22.5, 25.1, 29.1, 31.7, 36.7, 51.5, 71.1, 119.7, 150.6, 167.0. HPLC analysis (Whelk), Hex–EtOH; 95:5 (0.5 cm^3/min): (*S*)-**8** t_r=10.0 min, (*R*)-**8** t_r=10.5 min; 90% e.e.

4.1.3. *trans*-4*S*-Hydroxydec-2-enoic acid methyl ester 8. In an identical procedure to that described above, treatment of **5** (695 mg, 2.76 mmol) with AD mix-α followed by methyl diethylphosphonoacetate afforded the enantiomeric ester (*S*)-**8** (285 mg, 52%) as a clear liquid. $[\alpha]_D^{20}=+22.0$ ($c=1.00$, $CHCl_3$). HPLC analysis (Whelk), Hex–EtOH; 95:5 (0.5 cm^3/min): (*S*)-**8** $t_r=10.0$ min, (*R*)-**8** $t_r=10.5$ min; 90% e.e.

4.1.4. 5*R*-Hexyl-2(5*H*)-furanone 9.[27] At room temperature a solution of **5** (655 mg, 2.60 mmol, 1 equiv.) and $MeSO_2NH_2$ (309 mg, 3.25 mmol, 1.25 equiv.) in ^{t}BuOH (11 cm^3) and H_2O (11 cm^3) was treated with AD mix-β (10.4 g) for 24 h. DCM (25 cm^3) and H_2O (25 cm^3) were added and the mixture was partitioned for 0.5 h. The resultant aqueous layer was further extracted with DCM (4×25 cm^3) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude aldehyde. Under N_2, a solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (951 mg, 2.99 mmol, 1.15 equiv.) in THF (20 cm^3) was treated with 60% (w/w) NaH in mineral oil (111 mg, 2.78 mmol, 1.08 equiv.) at room temperature. After 0.5 h the solution was cooled to −78°C and the crude aldehyde in THF (5 cm^3) was added. The reaction was warmed to room temperature over 15 h. Et_2O (25 cm^3) and H_2O (25 cm^3) were added and the resultant aqueous layer was further extracted with Et_2O (3×25 cm^3). The combined extracts were dried over $MgSO_4$ before filtration and solvent removal gave a mixture of **8** and **9**. Purification by flash column chromatography (DCM–Hex; 1:1) afforded the furan-2(5*H*)-one **9** (101 mg, 23%) as a clear liquid, further elution (EtOAc) gave the ester **8** (97 mg, 19%) whose data was identical to that reported above. $R_f=0.15$ (DCM–Hex; 1:1); $[\alpha]_D^{20}=-84.1$ ($c=1.01$, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3057, 2930, 2859, 1752, 1601, 1467, 1266, 1165; *m*/*z* (CI) 186 (MNH_4^+, 100%), 169 (MH^+, 25%); found 169.12290, $C_{10}H_{16}O_2{\cdot}H$ requires 169.12286 (+0.3 ppm); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, $J=7.0$ Hz, CH_3), 1.25–1.36 (6H, m, CH_2), 1.38–1.48 (2H, m, CH_2), 1.60–1.79 (2H, m, CH_2), 5.01–5.13 (1H, m, CH), 6.09 (1H, dd, $J=1.75$, 6.0 Hz, CH), 7.44 (1H, dd, $J=1.5$, 6.0 Hz, CH); δ_C (100 MHz, $CDCl_3$) 13.9, 22.4, 24.9, 28.9, 31.5, 33.2, 83.4, 121.5, 156.2, 173.0. HPLC analysis (Whelk), Hex–EtOH; 95:5 (0.5 cm^3/min): (*S*)-**9** $t_r=16.7$ min, (*R*)-**9** $t_r=17.7$ min; 95% e.e.

4.1.5. 5*S*-Hexyl-2(5*H*)-furanone 9.[27] As described above, treatment of **5** (672 mg, 2.67 mmol) with AD-mix-α afforded the enantiomeric materials (*S*)-**9** (116 mg, 26%) and (*S*)-**8** (99 mg, 19%) following purification by flash column chromatography; $[\alpha]_D^{20}=+81.0$ ($c=1.00$, $CHCl_3$). HPLC analysis (Whelk), Hex–EtOH; 95:5 (0.5 cm^3/min): (*S*)-**9** $t_r=16.7$ min, (*R*)-**9** $t_r=17.7$ min; 88% e.e.

4.1.6. 2-Heptanoyl-5-hexyl-1,3-dioxolan-4-one 13. At room temperature a solution of **5** (1.99 g, 7.90 mmol, 1 equiv.) and $MeSO_2NH_2$ (0.94 g, 9.88 mmol, 1.25 equiv.) in ^{t}BuOH (30 cm^3) and H_2O (30 cm^3) was treated with AD mix-β (20.0 g) and vigorously stirred for a period of 2 days. DCM (75 cm^3) and H_2O (75 cm^3) were added and the resultant aqueous phase was further extracted with DCM (4×50 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resultant mixture was re-dissolved in DCM (30 cm^3) and 4 Å molecular sieves (2.0 g) were added. The mixture was stirred for 0.25 h before PDC (5.90 g, 15.68 mmol, 2.0 equiv.) was added. Stirring was continued for 2 h before silica (ca. 10 g) was added and the solvent removed in vacuo. The crude mixture was purified by flash column chromatography (Hex–EtOAc; 9:1) affording the acetal **13** (130 mg, 12%) as a colourless oil. $R_f=0.2$ (Hex–EtOAc; 9:1); ν_{max} (neat/cm^{-1}) 2957, 2929, 2859, 1807, 1737, 1467, 1379, 1309, 1199; *m*/*z* (ES^+) 339 (MNa^++MeOH, 100%), 307 (MNa^+, 10%); found 339.2133, $C_{17}H_{32}O_5{\cdot}Na$ requires 339.2147 (−4.3 ppm); found 307.1870, $C_{16}H_{28}O_4{\cdot}Na$ requires 307.1885 (−5.0 ppm); δ_H (400 MHz, $CDCl_3$); 0.86–0.92 (6H, m, CH_3), 1.26–1.38 (12H, m, CH_2), 1.43–1.53 (2H, m, CH_2), 1.58–1.66 (2H, m, CH_2), 1.72–1.82 (1H, m, CH_2), 1.88–1.99 (1H, m, CH_2), 2.60 (2H, t, $J=7.5$ Hz, CH_2), 4.32 (1H, ddd, $J=1.0$, 4.25, 7.5 Hz, CH), 5.48 (1H, d, $J=1.0$ Hz, CH); δ_C (100 MHz, $CDCl_3$) 13.95, 14.0, 22.4, 22.5, 22.6, 24.8, 28.65, 28.7, 30.9, 31.45, 31.5, 36.6, 74.3, 99.6, 171.7, 201.7.

4.1.7. [(*trans*-Hex-1-ene)-1-sulfonyl]benzene 17.[28] A solution of hexene (1.7 cm^3, 13.70 mmol, 1.5 equiv.) and phenyl vinyl sulfone (1.53 g, 9.10 mmol, 1 equiv.) in DCM (9 cm^3) was treated with **6** (386 mg, 0.46 mmol, 5 mol%). The mixture was heated to reflux under nitrogen for 15 h. Addition of silica (ca. 5 g) and solvent removal under reduced pressure and purification by flash column chromatography (Hex–EtOAc; 5:1) gave **17** (1.78 g, 87%) as a yellow liquid. $R_f=0.25$ (Hex–EtOAc; 5:1); *m*/*z* (CI) 242 (MNH_4^+, 100%), 225 (MH^+, 5%); found 242.12171, $C_{12}H_{16}O_2S{\cdot}NH_4$ requires 242.12148 (+1.0 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, $J=7.5$ Hz, CH_3), 1.32 (2H, sex, $J=7.5$ Hz, CH_2), 1.45 (2H, pent, $J=7.5$ Hz, CH_2), 2.33 (2H, dq, $J=1.5$, 7.5 Hz, CH_2), 6.32 (1H, dt, $J=1.5$, 15.0 Hz, CH), 6.98 (1H, dt, $J=7.5$, 15.0 Hz, CH), 7.53 (2H, t, $J=7.5$ Hz, ArH), 7.60 (1H, t, $J=7.5$ Hz, ArH), 7.87 (2H, d, $J=7.5$ Hz, ArH); δ_C (100 MHz, $CDCl_3$) 13.6, 22.2, 29.6, 31.1, 127.5, 129.2, 130.4, 133.1, 140.8, 147.2.

4.1.8. 5*R*-Butyl-2(5*H*)-furanone 20.[22,23] At 14°C a solution of vinyl sulfone **17** (893 mg, 3.99 mmol, 1 equiv.) and $MeSO_2NH_2$ (474 mg, 4.98 mmol, 1.25 equiv.) in ^{t}BuOH (20 cm^3) and H_2O (20 cm^3) was treated with AD mix-β (16.0 g). Stirring was continued for 24 h before DCM (50 cm^3) and H_2O (50 cm^3) were added. The mixture was vigorously partitioned for 0.5 h and the aqueous layer was further extracted with DCM (5×50 cm^3). The combined organic extracts were dried over $MgSO_4$. Filtration and solvent removal in vacuo gave the crude aldehyde **18**. Under N_2, at room temperature, a solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate in THF (20 cm^3) was treated with 60% w/w NaH in mineral oil (175 mg, 4.38 mmol, 1.1 equiv.). Stirring was continued for 0.25 h before the reaction was cooled to −78°C. A solution of the crude aldehyde **18** in THF (5 cm^3) was added and the mixture was stirred and warmed to room temperature over 15 h. Et_2O (25 cm^3) and H_2O (25 cm^3) were added and the resultant aqueous layer was further extracted with Et_2O (3×25 cm^3). The combined extracts were dried over $MgSO_4$ before filtration, solvent removal and purification by flash column chromatography (DCM–Hex; 3:1) gave **20**

(190 mg, 34%) as a clear liquid. R_f=0.25 (DCM–Hex; 3:1); $[\alpha]_D^{20}$=−103.0 (c=1.05, $CHCl_3$) {lit. $[\alpha]_D^{20}$=−99.0 (c=1.38, $CHCl_3$), 98% e.e.};[23] m/z (CI) 158 (MNH_4^+, 100%), 141 (MH^+, 40%); found 141.09155, $C_8H_{12}O_2{\cdot}H$ requires 141.09155 (0.00 ppm); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.0 Hz, CH_3), 1.28–1.49 (4H, m, CH_2), 1.60–1.79 (2H, m, CH_2), 4.96–5.04 (1H, m, CH), 6.07 (1H, dd, J=1.5, 5.5 Hz, CH), 7.44 (1H, dd, J=1.0, 5.5 Hz, CH); δ_C (100 MHz, $CDCl_3$) 13.7, 22.3, 26.9, 32.8, 83.3, 121.4, 156.3, 173.0.

4.1.9. *trans*-4*R*-Hydroxyoct-2-enoic acid methyl ester 19. Further elution (EtOAc) gave the ester **19**, which was re-purified by flash column chromatography (Hex–EtOAc; 3:1) and isolated (131 mg, 19%) as a clear liquid. R_f=0.2 (Hex–EtOAc; 3:1); $[\alpha]_D^{20}$=−21.0 (c=1.00, $CHCl_3$) {lit. $[\alpha]_D^{20}$=−18.3 (c=1.05, $CHCl_3$), 73% e.e.};[15] m/z (CI) 190 (MNH_4^+, 100%), 173 (MH^+, 50%), 141 ($M-OCH_3^+$, 55%); found 173.11715, $C_9H_{16}O_3{\cdot}H$ requires 173.11777 (−3.8 ppm); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J=7.0 Hz, CH_3), 1.28–1.45 (4H, m, CH_2), 1.53–1.62 (2H, m, CH_2), 2.16 (1H, s(br), OH), 3.72 (3H, s, CH_3), 4.27–4.53 (1H, m, CH), 6.03 (1H, d, J=15.5 Hz, CH), 6.95 (1H, dd, J=5.0, 15.5 Hz, CH); δ_C (100 MHz, $CDCl_3$) 13.8, 22.5, 27.3, 36.3, 51.5, 71.0, 119.6, 150.3, 167.0.

4.1.10. 5*R*-Butyl-4*S*-methyl-dihydrofuran-2-one (quercus lactone) 21.[22] Under N_2, a slurry of CuI (223 mg, 1.17 mmol, 1.6 equiv.) in Et_2O (10 cm^3) was treated with 1.6 M MeLi in hexanes (1.55 cm^3, 2.48 mmol, 3.3 equiv.) at −78°C. Stirring was continued for 1 h, during which period the temperature rose to 0°C. The solution of Me_2CuLi was re-cooled to −78°C and **20** (105 mg, 0.75 mmol, 1 equiv.) in Et_2O (2 cm^3) was added. Stirring was continued for 1 h at −78°C to −20°C. Saturated NH_4Cl (25 cm^3) was added and the mixture was extracted with Et_2O (3×25 cm^3). The combined organic extracts were dried over $MgSO_4$. Filtration, solvent removal in vacuo and purification by flash column chromatography (Hex–EtOAc; 3:1) gave the lactone **21** (78 mg, 67%) as a pale yellow oil. R_f=0.3 (Hex–EtOAc; 3:1); $[\alpha]_D^{20}$=+77.4 (c=0.93, MeOH) {lit. $[\alpha]_D^{21}$=+79.9 (c=1.01, MeOH)};[22c] m/z (CI) 174 (MNH_4^+, 100%), 157 (MH^+, 70%); found 157.12322, $C_9H_{16}O_2{\cdot}H$ requires 157.12286 (+2.4 ppm); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, J=7.0 Hz, CH_3), 1.14 (3H, d, J=6.5 Hz, CH_3), 1.28–1.43 (2H, m, CH_2), 1.43–1.72 (4H, m, CH_2), 2.14–2.25 (2H, m, CH_2,CH), 2.61–2.71 (1H, m, CH_2), 4.01 (1H, ddd, apparent dt, J=4.0, 7.75 Hz, CH); δ_C (100 MHz, $CDCl_3$) 13.7, 17.4, 22.4, 27.7, 33.6, 35.9, 37.0, 87.3, 176.4.

4.1.11. 9-Decenoic acid 23.[29] At room temperature, a solution of 9-decen-1-ol **22** (4.57 cm^3, 25.6 mmol, 1 equiv.) and PDC (38.52 g, 102.4 mmol, 4 equiv.) in DMF (75 cm^3) was stirred for 10 h. Water (500 cm^3) and ether (150 cm^3) were added. The resultant aqueous layer was extracted with ether (2×150 cm^3). The combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude acid. Purification by flash column chromatography (Hex–EtOAc; 5:1) gave the acid **23** (3.02 g, 69%) as a yellow oil. R_f=0.15 (Hex–EtOAc; 3:1); m/z (CI) 188 (MNH_4^+, 100%), found 188.16519, $C_{10}H_{18}O_2{\cdot}NH_4$ requires 188.16505 (+0.8 ppm); δ_H (400 MHz, $CDCl_3$) 1.30–1.44 (8H, m, CH_2), 1.61–1.69 (2H, m, CH_2), 2.02–2.08 (2H, m, CH_2), 2.36 (2H, t, J=7.5 Hz, CH_2), 4.92–5.03 (2H, m, CH_2), 5.76–5.87 (1H, m, CH), 11.15 (1H, s(br), OH); δ_C (100 MHz, $CDCl_3$) 24.7, 28.8, 28.9, 29.0, 29.05, 33.7, 33.9, 114.2, 139.1, 179.4.

4.1.12. Ethyl 9-decenoate 24. A solution of the acid **23** (3.02 g, 17.74 mmol, 1 equiv.) in EtOH (45 cm^3) was treated with concentrated sulphuric acid H_2SO_4 (ca. 0.5 cm^3). The mixture was heated to reflux for 22 h. Ether (80 cm^3) and a saturated aqueous solution of $NaHCO_3$ (80 cm^3) were added. The resultant aqueous layer was extracted with ether (2×80 cm^3). The combined organic extracts were washed with water (100 cm^3) and dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude ester. Purification by flash column chromatography (Hex–EtOAc; 19:1) gave the ester **24** (3.26 g, 93%) as a yellow oil. R_f=0.3 (Hex–EtOAc; 19:1); ν_{max} (neat/cm^{-1}) 3076, 2978, 2928, 2855, 1738, 1641; m/z (CI) 216 (MNH_4^+, 10%), 199 (MH^+, 100%), found 199.17025, $C_{12}H_{22}O_2{\cdot}H$ requires 199.16980 (+2.5 ppm); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, J=7.0 Hz, CH_3), 1.29–1.36 (6H, m(br), CH_2), 1.34–1.43 (2H, m(br), CH_2), 1.58–1.67 (2H, m, CH_2), 2.01–2.08 (2H, m, CH_2), 2.29 (2H, t, J=7.5 Hz, CH_2), 4.13 (2H, q, J=7.0 Hz, CH_2), 4.92–5.03 (2H, m, CH_2), 5.76–5.86 (1H, m, CH); δ_C (100 MHz, $CDCl_3$) 13.9, 24.6, 28.5, 28.6, 28.8, 33.5, 34.1, 60.0, 114.4, 139.5, 174.4; found C, 72.89; H, 11.47%, $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.18%.

4.1.13. (*trans*)-10-Benzenesulfonyl-dec-9-enoic acid ethyl ester 25. Under N_2, a solution of ester **24** (2.17 g, 10.93 mmol, 1 equiv.), phenyl vinyl sulfone (1.84 g, 10.93 mmol, 1 equiv.) and **6** (0.464 g, 0.55 mmol, 5 mol%) in CH_2Cl_2 (22 cm^3) was heated to reflux for 18 h. Silica (ca. 5 g) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography (Hex–EtOAc; 3:1) gave the product **25** (3.30 g, 89%) as a viscous yellow oil. R_f=0.2 (Hex–EtOAc; 3:1); ν_{max} (neat/cm^{-1}) 3058, 2980, 2931, 2856, 1732, 1625, 1319, 1147; m/z (CI) 357 (MNH_4^+, 35%), 339 (MH^+, 85%), found 339.16236, $C_{18}H_{26}O_4S{\cdot}H$ requires 339.16299 (−2.0 ppm); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, J=7.0 Hz, CH_3), 1.26–1.33 (8H, m, CH_2), 1.41–1.50 (2H, m, CH_2), 1.56–1.64 (2H, m, CH_2), 2.19–2.30 (2H, m, CH_2), 4.12 (2H, q, J=7.0 Hz, CH_2), 6.31 (1H, dt, J=1.5, 15.0 Hz, CH), 6.98 (1H, dt, J=6.75, 15.0 Hz, CH), 7.50–7.63 (3H, m, ArH), 7.86–7.90 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.2, 24.8, 27.5, 28.8, 28.9, 28.95, 31.4, 34.3, 60.2, 127.6, 129.2, 130.5, 133.2, 140.9, 147.1, 173.7; found C, 63.71; H, 7.77%, $C_{18}H_{26}O_4S$ requires C, 63.88; H, 7.74%.

4.1.14. 8-(5*R*-Oxo-2,5-dihydrofuran-2-yl)octanoic acid ethyl ester (maritolide) 26.[24] At room temperature, a solution of **25** (850 mg, 2.51 mmol, 1 equiv.) and $MeSO_2$-NH_2 (299 mg, 3.14 mmol, 1.25 equiv.) in ^tBuOH (11 cm^3) and H_2O (11 cm^3) was treated with AD mix-β (10 g) for 66 h. DCM (40 cm^3) and water (40 cm^3) were added and the mixture was partitioned for 0.5 h. The resultant aqueous layer was further extracted with DCM (4×25 cm^3) and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude aldehyde. Under N_2, a solution

of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (0.61 cm^3, 2.89 mmol, 1.15 equiv.) in THF (20 cm^3) was treated with 60% w/w NaH in mineral oil (109 mg, 2.73 mmol, 1.08 equiv.) at room temperature. After 0.5 h, the solution was cooled to −78°C and the crude aldehyde in THF (5 cm^3) was added. The reaction was allowed to warm to room temperature over 18 h, whereupon, Et_2O (25 cm^3) and H_2O (25 cm^3) were added and the resultant aqueous layer was further extracted with Et_2O (3×25 cm^3). The combined extracts were dried over $MgSO_4$ before filtration and solvent removal gave a mixture of **26** and **27**. Initial purification by flash column chromatography (DCM–EtOAc; 15:1) allowed the separation of **26** [R_f=0.45 (DCM–EtOAc; 15:1)] and **27** [R_f=0.15 (DCM–EtOAc; 15:1)]. Further, purification by flash column chromatography (Hex–EtOAc; 3:1) afforded the lactone **26** (178 mg, 28%) as a pale yellow oil (amorphous solid at −5°C). R_f=0.10 (Hex–EtOAc; 3:1); $[\alpha]_D^{25}=-58.6$ (c=0.99, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3087, 2933, 2858, 1732, 1601; m/z (CI) 255 (MH^+, 100%), found 255.15981, $C_{14}H_{22}O_4$·H requires 255.15964 (+0.7 ppm); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, J=7.0 Hz, CH_3), 1.28–1.37 (6H, m, CH_2), 1.39–1.47 (2H, m, CH_2), 1.58–1.80 (4H, m, CH_2), 2.28 (2H, t, J=7.5 Hz, CH_2), 4.12 (2H, q, J=7.0 Hz, CH_2), 5.00–5.05 (1H, m, CH), 6.10 (1H, dd, J=2.0, 5.75 Hz, CH), 7.46 (1H, dd, J=1.5, 5.75 Hz, CH); δ_C (100 MHz, $CDCl_3$) 14.3, 24.85, 24.9, 28.9, 29.0, 29.1, 33.2, 34.3, 60.2, 83.3, 121.6, 156.1, 173.8. HPLC analysis (Chiralpak AD), Hex–EtOH; 90:10 (1.0 cm^3/min): (*R*)-**26** t_r=15.1 min, (*S*)-**26** t_r=19.4 min; 96% e.e.

4.1.15. (*trans*)-4*R*-Hydroxy-dodec-2-enedioic acid 12-ethyl ester 1-methyl ester 27. Similarly, re-purification by flash column chromatography (Hex–EtOAc; 2:1) afforded the alcohol **27** (91 mg, 13%) as a colourless oil. R_f=0.2 (Hex–EtOAc; 2:1); $[\alpha]_D^{25}=-16.8$ (c=1.01, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3450, 2933, 2856, 1728, 1659; m/z (CI) 287 (MH^+, 100%), found 287.18630, $C_{15}H_{26}O_5$·H requires 287.18585 (+1.6 ppm); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, J=7.0 Hz, CH_3), 1.29–1.70 (12H, m, CH_2), 2.28 (2H, t, J=7.5 Hz, CH_3), 3.75 (3H, s, CH_3), 4.13 (2H, q, J=7.0 Hz, CH_2), 4.26–4.35 (1H, s(br), CH), 6.04 (1H, dd, J=1.5, 15.75 Hz, CH), 6.95 (1H, dd, J=5.0, 15.75 Hz, CH); δ_C (100 MHz, $CDCl_3$) 14.3, 24.9, 25.1, 29.0, 29.05, 29.2, 34.3, 36.7, 51.6, 60.2, 71.1, 119.8, 150.3, 166.1, 173.8. HPLC analysis (Whelk), Hex–EtOH; 95:5 (1.0 cm^3/min): (*S*)-**27** t_r=20.8 min, (*R*)-**27** t_r=22.3 min; 97% e.e.

4.1.16. 8-(5*S*-Oxo-2,5-dihydrofuran-2-yl)octanoic acid ethyl ester (maritolide) 26.[24] Following the procedure described above, **25** (850 mg, 2.51 mmol) was treated with AD mix-α then the phosphonate affording (*S*)-**26** (143 mg, 22%) as a colourless oil. Data as described for (*R*)-**26**; $[\alpha]_D^{25}=+63.4$ (c=1.02, $CHCl_3$). HPLC analysis (Chiralpak AD), Hex–EtOH; 90:10 (1.0 cm^3/min): (*R*)-**26** t_r=15.1 min, (*S*)-**26** t_r=19.4 min; 95% e.e.

4.1.17. (*trans*)-4*S*-Hydroxy-dodec-2-enedioic acid 12-ethyl ester 1-methyl ester 27. As above, the corresponding alcohol (*S*)-**27** (97 mg, 13%) was also isolated as a colourless oil. Data as described for (*R*)-**27**; $[\alpha]_D^{25}=+16.7$ (c=0.96, $CHCl_3$). HPLC analysis (Whelk), Hex–EtOH; 95:5 (1.0 cm^3/min): (*S*)-**27** t_r=20.8 min, (*R*)-**27** t_r=22.3 min; 93% e.e.

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