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Synthesis and olfactory properties of unnatural derivatives of lilac aldehydes

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ABSTRACT

Lilac aldehydes are considered as principal olfactory molecules of lilac flowers. We have designed, prepared and evaluated two sets of their unnatural racemic analogues as pure diastereomers. While the synthesis of *gem*-dimethyl homologues starts from geranyl acetate, the preparation of methylene derivatives commences from linalyl acetate. The key Lewis and/or Brønsted acid catalysed cyclisation furnishes easily separable *cis*-/*trans*-tetrahydrofuranyl esters as common advanced intermediates. The subsequent functional group transformations lead to target aldehydes, alcohols, nitriles and olefins. Unlike the homologues possessing similar herbal scents, methylene derivatives exhibit woody and/or flowery odours. In the latter case, the sensory evaluation suggests the importance of relative stereochemistry and/or type of functional group on the odour character of respective compounds.

1. Introduction

Lilac aldehydes[1] **1** (Fig. 1) are naturally occurring monocyclic tetrahydrofuranyl terpenes considered as principal olfactory molecules of lilac flowers (*Syringa vulgaris* L., Oleaceae). Their biogenetic formation from isopentenyl diphosphate and dimethylallyl diphosphate was proposed and investigated.[2] Various diastereomers of lilac aldehydes were also found in mixtures of volatile components from numerous plant species including flowers of kiwifruit[3a] (*Actinidia arguta*), White Campion[3b] (*Silene latifolia*), and Lesser Butterfly orchid (*Platanthera bifolia*).[3c] Thus not surprisingly, lilac aldehydes are of special interest for pollinators. It is known that these monoterpenes are highly attractive to the (nocturnal) moth species[4] as well as butterflies.[5] Despite the unique olfactory characteristics of lilac, until now there is no commercially available lilac flower oil, although many attempts have been made to produce satisfactory lilac concentrates.[6] Because no natural lilac flower oil is being produced so far, synthetically prepared lilac aldehydes are used in perfumery. Interestingly, the major naturally occurring (5′*S*)-stereoisomers **1a**–**d** have the odour threshold lower by 1–2 orders of magnitude in comparison to lilac aldehydes **1e**–**h** with (5′*R*)-absolute configuration[7] (Fig. 1).

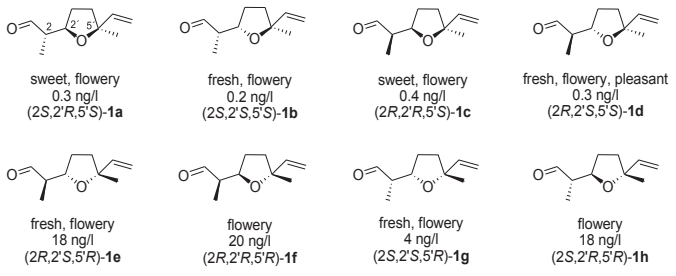

Fig. 1. Structures of lilac aldehydes **1a**–**h** with their odour thresholds.

There are numerous syntheses of racemic[3a,4b,8] and enantiomerically pure[7,9] lilac aldehydes **1** known to date. To the best of our knowledge, however, there is no comprehensive study available that would investigate the importance of respective substituents on the genuine flowery odour of lilac aldehydes. Therefore, we have designed and prepared two racemic sets of unnatural derivatives of lilac aldehydes: while the first one comprises diastereomerically pure *gem*-dimethyl homologues **2**–**7** (Fig. 2), the second one consists of methylene analogues **8**–**10** (Fig. 3). All of these novel derivatives feature a lower degree of asymmetry by having only two instead of naturally three stereogenic centres, either due to the incorporation of additional methyl group at the C-2 position or, conversely, removal of the existing one. In the first case, such a homologation also prevents otherwise feasible enolisation of

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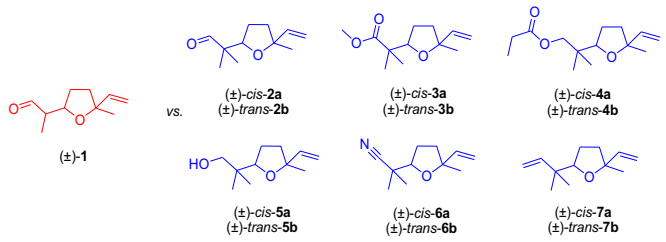


Fig. 2. Homologated unnatural derivatives **2**–**7** of lilac aldehydes **1**.

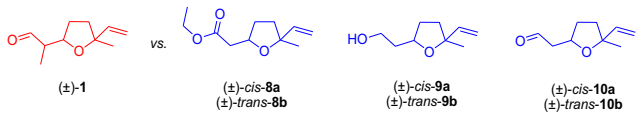


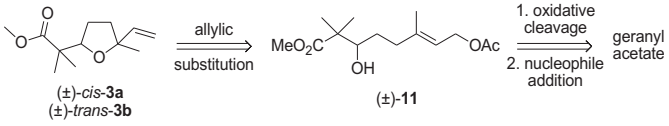
Fig. 3. Demethylated unnatural derivatives **8**–**10** of lilac aldehydes **1**.

a carbonyl group that might, however, negatively influence the stability of the fragrance molecules. Moreover, we have also replaced the original aldehydic group of **1** for esters **3**, **4** and **8**, alcohols **5** and **9**, nitrile **6** and olefin **7** (Figs. 2 and 3).

2. Results and discussion

2.1. Retrosynthetic analysis of homologues 2–7

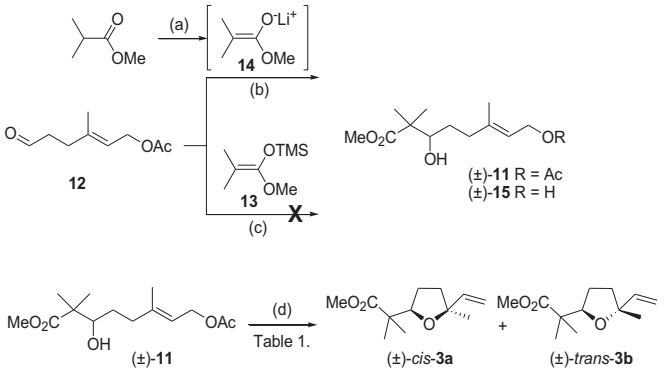
The retrosynthetic analysis of racemic C-2 homologues **2**–**7** relies on diastereomerically pure methylesters (±)-**3** as common synthetic intermediates. These key building blocks are, in turn, readily accessible from commercially available geranyl acetate via initial epoxidation[10]–cleavage[11]–addition[12] sequence followed by cyclisative allylic *O*-substitution[13] of hydroxydiester (±)-**11** (Scheme 1).



Scheme 1. Retrosynthetic analysis of key intermediates (±)-**3**.

2.2. Synthesis of homologues 2–7

The synthesis of racemic homologues **2**–**7** starts with the known[14] aldehyde **12** prepared by a two-step protocol[15] from geranyl acetate. The subsequent nucleophilic addition[12] of in situ prepared ketene acetal required considerable experimentation. While the silylated enol ether **13** did not furnish the desired product at all (zero conversion of **12** even at rt), the low temperature addition of lithium enolate **14** led to the hydroxydiester (±)-**11**. However, the (isolated) yield of the adduct was strongly dependent on the amount of nucleophile. While the use of 1.5 M equiv of **14** led to the incomplete (75%) conversion of aldehyde **12**, addition of 1.85 M equiv of ketene acetal to **12** furnished mainly the dihydroxyester (±)-**15** as a product of in situ deacetylation[16] of initially formed adduct (±)-**11**. Thus, the optimised protocol involved addition of 1.65 M excess of lithium enolate **14** to aldehyde **12** at −85 °C to obtain the desired hydroxydiester (±)-**11** in 65% yield after FLC (Scheme 2). This compound was subsequently used for the key cyclisative allylic substitution (Table 1). Among Lewis acids tested, bismuth(III) triflate[17] afforded the highest combined yield of desired methylesters (±)-**3** (85%). Analogously, the Brønsted-type triflic acid[18] also furnished tetrahydrofuranyl esters (±)-**3** in high yield. However, the diastereoselectivity in both cases was poor (cis/trans ~ 1:1.3). Nevertheless, racemic diastereomers were (partially) separable by careful flash chromatography on silica gel. The relative configurations of (±)-*cis*-**3a** and (±)-*trans*-**3b** were assigned on the basis of 1D NOESY spectra (Fig. 4).



Scheme 2. Reagents and conditions: (a) *n*-BuLi, *i*-Pr_2NH, methyl-2-methylpropionate, THF, 0 °C, 2 h; (b) **14** (1.65 equiv), THF, −85 °C, 2 h, FLC (65% (±)-**11**); (c) **13** (2 equiv), DCM, −80 °C to rt, 7 d (0% conversion of **12**); (d) Lewis/Brønsted acid (0.015–0.1 equiv), DCM (see Table 1).

Subsequently, pure diastereomers (±)-*cis*-**3a** and (±)-*trans*-**3b** were transformed to racemic targets **2**, **4**–**7**. Thus, hydride reduction[19] of separated methylesters (±)-**3** furnished the homologues of lilac alcohols (±)-*cis*-**5a** and (±)-*trans*-**5b** in practically quantitative yield (Scheme 3). Next, alcohols (±)-*cis*-**5a** and (±)-*trans*-**5b** were: (a) oxidised[20] to homologues of lilac aldehydes (±)-*cis*-**2a** and (±)-*trans*-**2b**; (b) acylated[21] with propanoic anhydride to esters (±)-*cis*-**4a** and (±)-*trans*-**4b** in high yields. Finally, the aldehydes (±)-*cis*-**2a** and (±)-*trans*-**2b** were transformed to: (a) nitriles (±)-*cis*-**6a** and (±)-*trans*-**6b** via intermediary imines using iodine in aq ammonia at sub-zero temperature;[22] (b) dienes (±)-*cis*-**7a** and (±)-*trans*-**7b** via Wittig reaction[23] in good to high yields (Scheme 3).

2.3. Retrosynthetic analysis of analogues 8–10

Having prepared the set of homologated derivatives **2**–**7** of lilac aldehydes **1**, we turned our attention to the synthesis of racemic C-2 demethylated analogues **8**–**10**. Their retrosynthetic analysis relies on diastereomerically pure ethylesters (±)-**8** as common synthetic intermediates. These key building blocks are, in turn, readily accessible from commercially available linalyl acetate via initial epoxidation[10]–oxidative cleavage[11]–Wittig olefination[24] sequence followed by Zemplen deacetylation of diester (±)-**16** with concomitant in situ base catalysed cyclisative Michael addition[25] (Scheme 4).

2.4. Synthesis of analogues 8–10

The synthesis of racemic analogues **8**–**10** starts with the known[26] aldehyde (±)-**17** prepared by two-step protocol[27] from linalyl acetate. The Wittig olefination[24] of (±)-**17** with commercially available phosphorane **18** furnished exclusively (*E*)-configured unsaturated diester (±)-**16** in moderate yield. Subsequently, its allylic acetate was deacetylated with sodium ethoxide to provide a corresponding allylic alcohol. This intermediate underwent in situ intramolecular 1,4-conjugate addition[28] to the unsaturated ester moiety to furnish desired tetrahydrofurans (±)-**8**, however, in moderate combined yield and non-stereoselectively (Scheme 5).[29] Nevertheless, racemic diastereomers were (partially) separable by careful flash chromatography on silica gel. The relative configurations of (±)-*cis*-**8a** and (±)-*trans*-**8b** were assigned on the basis of 1D NOESY spectra (Fig. 5).

Table 1
Screening of cyclisative allylic *O*-substitution of hydroxydiester (±)-**11** in Scheme 2

Catalyst (10 mol %)	Temperature, time	Conversion[c] of (±)-**11**	Ratio[d] of (±)-*cis*-**3a**/(±)-*trans*-**3b**	Combined yield[e] of (±)-**3** (%)
$Bi(OTf)_3$[a]	0 °C to rt, 1 h	100%	1:1.3	85
$In(OTf)_3$	−20 °C to rt, 1 d	100%	1:1.1	52
$Sc(OTf)_3$	−20 °C to 35 °C, 5 d	100%	1:1.05	54
$Al(OTf)_3$	0 °C to 35 °C, 7 d	Incomplete conversion (ca. 80%)	—	—
$Y(OTf)_3$	0 °C to rt, 7 d	No conversion	—	—
TfOH[b]	rt, 30 min	100%	1:1.3	89
$Pd(PPh_3)_4$	50 °C, 7 d	Incomplete conversion (ca. 40%)	—	—

[a] Catalyst of 3 mol % was used.
[b] Catalyst of 1.5 mol % was used.
[c] TLC control.
[d] Determined by LC–MS analyses of crude reaction mixtures.
[e] After FLC.

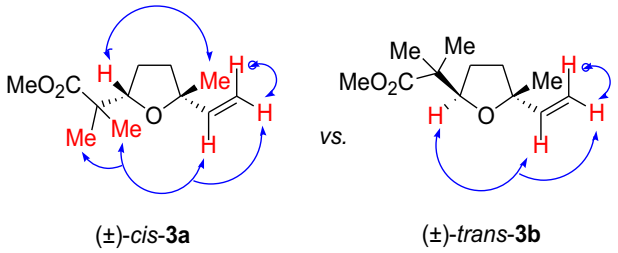
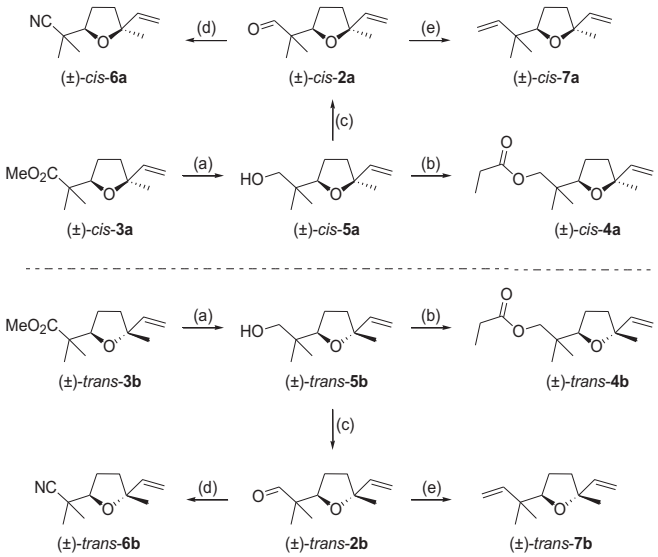
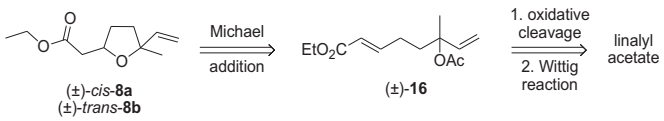


Fig. 4. 1D NOESY interactions of (±)-*cis*-**3a** and (±)-*trans*-**3b**.

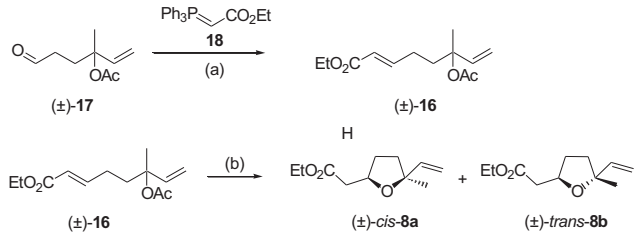


Scheme 3. Reagents and conditions: (a) $LiAlH_4$ (2 equiv), Et_2O, 0 °C, 30 min (99% (±)-**5**); (b) cat. DMAP, $(EtCO)_2O$ (2.5 equiv), Et_3N (3.5 equiv), DCM, 0 °C, 2 h, FLC (80% (±)-**4**); (c) PCC (1.5 equiv), 4 Å MS, DCM, 0 °C, 6 h, FLC (80% (±)-**2**); (d) I_2 (3 equiv), THF/aq NH_3 (1.5:1), −10 °C, 2 h, FLC (86% (±)-**6**); (e) $MePPh_3^+Br^-$ (2 equiv), BuLi (1.9 equiv), THF, 0 °C, 1 h, FLC (70% (±)-**7**).



Scheme 4. Retrosynthetic analysis of key intermediates (±)-**8**.

Finally, pure diastereomers (±)-*cis*-**8a** and (±)-*trans*-**8b** were transformed to racemic targets **9** and **10**. Thus, analogously to the previous set, hydride reduction[19] of separated ethylesters (±)-**8** furnished C-2 demethylated analogues of lilac alcohols (±)-*cis*-**9a** and (±)-*trans*-**9b** in high yield. Eventually, their oxidation furnished C-2 demethylated analogues of lilac aldehydes (±)-**10** (Scheme 6).



Scheme 5. Reagents and conditions: (a) **18** (1.2 equiv), DCM, 0 °C, 1 h, FLC (52% (±)-**16**); (b) EtONa (1.1 equiv), EtOH, 0 °C to rt, 3 h, FLC (54% (±)-**16**, dr ~ 1:1).

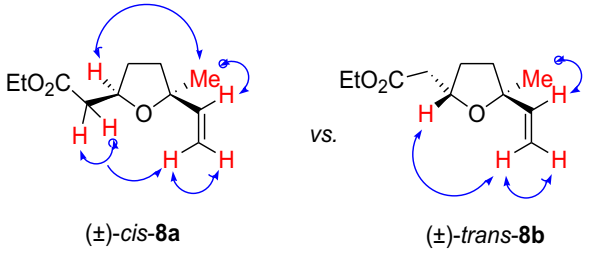
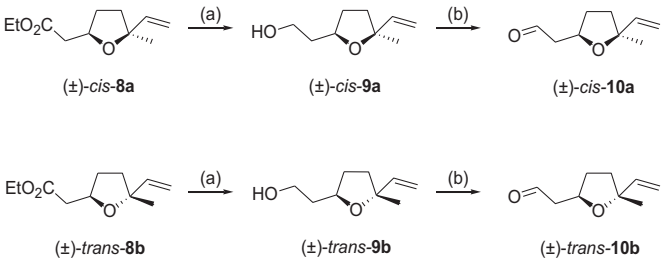


Fig. 5. 1D NOESY interactions of (±)-*cis*-**8a** and (±)-*trans*-**8b**.



Scheme 6. Reagents and conditions: (a) $LiAlH_4$ (2 equiv), Et_2O, 0 °C, 30 min, FLC (89% (±)-**9**); (b) PCC (1.5 equiv), 4 Å MS, DCM, 0 °C to rt, 13 h, FLC (72% (±)-**10**).

However, partial C-3 epimerisation of both aldehydes took place under these conditions, and thus, we have finally obtained diastereomeric mixtures of (±)-*cis*-**10a** (dr 2.5:1) and (±)-*trans*-**10b** (dr 4.5:1).

2.5. Olfactory evaluation

With both sets of racemic and diastereomerically pure unnatural analogues **2**–**10** in hands, we have undertaken their sensory evaluation. In the first series, all except one C-2 *gem*-dimethyl homologues **2**–**7** exhibited a fresh camphoraceous-minthy-eucalypty scent. However, this common olfactory feature was significantly accompanied by coconut notes in the case of aldehyde (±)-*cis*-**2a**. Analogous though less pronounced coconut note was

also observed in ester (±)-*trans*-**4b**. The only compound that scented slightly differently from their counterparts was its diastereomer (±)-*cis*-**4a**, which exhibited a weak minty scent with fresh coconut note. These results suggest two implications for structure–olfactory relationship: (a) addition of methyl group to C-2 stereogenic centre of lilac aldehydes **1** significantly shifts the original flowery odour to rather herbal scent of their unnatural homologues **2** (Fig. 6); (b) various functional groups (ester, aldehyde, alcohol, nitrile, olefin) have only minimal, if any, effect on the scent variations within the group of homologues **2**–**7**; (c) relative configuration has similarly negligible influence on the scent variations within diastereomeric pairs with some exception for esters (±)-**4**.

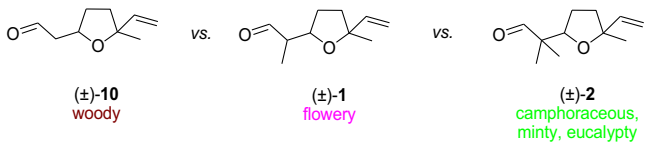


Fig. 6. Influence of C-2 substitution on the olfactory properties of lilac aldehydes **1** versus their unnatural homologues **2** and analogues **10**.

Conversely, the olfactory analysis in second series revealed not only broader spectrum of odours but also significant effect of the functional group and/or relative configuration on the scent of C-2 demethylated derivatives **8**–**10**. Thus, while the aldehyde (±)-*cis*-**10a** exhibits strong fresh woody odour (Fig. 6), its diastereomer (±)-*trans*-**10b** possesses sweet woody scent with coconut tone. The reduction of aldehydic group slightly shifted the woody scent of alcohol (±)-*cis*-**9a** towards the flowery note, while its diastereomer (±)-*trans*-**9b** features fresh camphoraceous scent with coconut note. Eventually, both esters (±)-**8** are lacking woody aspects too, and exhibit instead either fresh flowery odour ((±)-*trans*-**8a**) or spicy flowery scent ((±)-*cis*-**8a**). Such results imply an important role of both relative stereochemistry as well as nature of C-1 substituent on the odour character of analogues **8**–**10**. Moreover, and again, this observation points to the crucial olfactory role of the stereogenic centre at C-2 of naturally occurring lilac aldehydes **1**. Finally, the odour persistence (sensoric tenacity) for all tested compounds **2**–**10** falls in the range of 6–8 h.

3. Conclusion

We have designed two racemic sets of diastereomerically pure unnatural analogues **2**–**10** of lilac aldehydes **1**. Thus, starting from geranyl acetate, we have prepared diastereomerically pure aldehydes (±)-**2**, esters (±)-**3** and (±)-**4**, alcohols (±)-**5**, nitriles (±)-**6** and olefins (±)-**7** via catalytic activation[30] of allylic acetate (±)-**11**. On the other hand, by employing linalyl acetate, we have synthetised diastereomerically pure ethyl esters (±)-**8**, alcohols (±)-**9**, and aldehydes (±)-**10**. The relative configurations of key tetrahydrofuranyl (m)ethyl esters (±)-*cis*-**3a**/**8a** and (±)-*trans*-**3b**/**8b** as common synthetic intermediates were determined by 1D NOESY experiments. The olfactory analysis revealed that while C-2 dimethylated homologues **2**–**7** exhibit similar herbal scents, the corresponding C-2 demethylated derivatives **8**–**10** possess a broader range of scents with woody and/or flowery odours as dominant. Unlike with homologues **2**–**7**, the nature of C-1 substituent and/or relative stereochemistry has significant effect on the scent variations within the group of analogues **8**–**10**. Finally, our results suggest that both installation and removal of methyl group at C-2 significantly alters the olfactory properties of such unnatural derivatives **2**–**10** in comparison to their parent structures **1**.

4. Experimental section

4.1. General

All reactions (except for the preparation of nitriles ((±)-**6**) were carried out under argon using standard techniques for the exclusion of air. All solvents of p.a. purity were dried over 4 Å molecular sieves. All reagents were purchased and used as received without further purification. Infrared (IR) spectra were recorded on an FTIR spectrometer Nicolet 5700 as films on a diamond sampler (ATR) or as films on KBr. NMR spectra were obtained in $CDCl_3$ on a Varian VXR-300 instrument. Proton chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS as an internal reference and carbon chemical shifts are reported in parts per million (ppm) relative to the centre line of the $CDCl_3$ triplet (77.16 ppm). Analytical TLC was performed on Silica Gel 60 F-254 plates and visualised with aqueous $KMnO_4$. Flash column chromatography was performed using silica gel (Kieselgel 60 (40–63 μm). HRMS spectra were recorded either on a TOF-Q instrument and evaluated using Compass DataAnalysis 4.0 software or Orbitrap Velos Pro instrument and evaluated using Xcalibur 2.7 SP1 software. LC–MS analyses were performed on the instrument equipped with a multimode MS detector using the MM ESI/APCI ionisation method (column Zorbax Eclipse XDB-18 150×4.6 mm, particle size 5 μm, eluent water with 0.1% HCO_2H/CH_3CN, 70:30, flow 1.5 mL/min).

4.2. Synthetic procedures

*4.2.1. (E)-Methyl 8-acetoxy-3-hydroxy-2,2,6-trimethyloct-6-enoate (±)-**11**.* BuLi (7.2 mL, 17.28 mmol, 2.4 M in hexanes) was added dropwise to a stirred solution of diisopropylamine (1.725 g, 17.05 mmol) in dry THF (6.5 mL) at −5 °C. This mixture was stirred for 30 min and then methyl isobutyrate (1.741 g, 16.712 mmol) was added dropwise. Mixture was cooled to −85 °C, stirred for 1 h and anhydrous THF (110 mL) was added. Aldehyde **12** (1.724 g, 10.1287 mmol) in dry THF (5 mL) was added dropwise to the mixture over 10 min. The mixture was stirred for 2 h and then quenched with 10% aq HCl (15 mL) and H_2O (50 mL), warmed to room temperature and extracted with Et_2O (3×35 mL). Combined organic layers were washed with H_2O (50 mL) and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue (3 g) was purified by FLC (90 g SiO_2, Et_2O/hexanes 1:4) to afford compound (±)-**11** as a pale yellow oil (1.8 g, 65%); R_f 0.42 (EtOAc/hexanes 2:5); IR (ATR) ν_{max} 3506, 2978–2951 (br), 1717, 1674, 1468, 1435, 1385, 1366, 1230, 1134, 1021, 950 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.16, 1.18 (6H, 2×s, 2×CH_3C), 1.28–1.63 (2H, m, CH_2CHOH), 1.71 (3H, s, CH_3C=CH), 2.06 (3H, s, CH_3CO); 2.07–2.41 (2H, m, CH_2CH=C), 2.51 (1H, br s, CHO*H*, exchange with D_2O), 3.58 (1H, d, *J* 10.5 Hz, C*H*OH), 3.70 (3H, s, CO_2Me), 4.59 (2H, d, *J* 7 Hz, CH_2OCOCH_3), 5.31–5.42 (1H, m, C*H*=C); δ_C (75 MHz, $CDCl_3$) 16.6, 20.6, 22.5, 21.2, 29.7, 36.6, 47.3, 52.0, 61.4, 76.3, 118.8, 142.1, 171.2, 178.3; HRMS (ESI-TOF): MK^+, calculated for $C_{14}H_{24}O_5K^+$ 311.1261, found 311.1225.

*4.2.2. (E)-Methyl 3,8-dihydroxy-2,2,6-trimethyloct-6-enoate (±)-**15**.* R_f 0.31 (hexanes/EtOAc 3:2); IR (ATR) ν_{max} 3495, 2978–2951 (br), 1720, 1464, 1434, 1383, 1365, 1270, 1188, 1135, 1080, 979 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.18, 1.20 (6H, 2×s, 2×CH_3C), 1.29–1.63 (2H, m, CH_2CHOH), 1.70 (3H, s, CH_3C=CH), 2.07–2.41 (2H, m, CH_2CH=C), 2.55 (1H, br s, CHO*H*, exchange with D_2O), 3.58 (1H, d, *J* 9.2 Hz, C*H*OH), 3.70 (3H, s, CO_2Me), 4.16 (2H, m, CH_2OH), 5.38–5.50 (1H, m, C*H*=C); δ_C (75 MHz, $CDCl_3$) 16.4, 20.6, 22.8, 29.8, 36.6, 47.3, 52.2, 59.4, 76.3, 123.9, 139.5, 178.3.

*4.2.3. Methyl 2-methyl-2-(5′-methyl-5′-vinyltetrahydrofuran-2′-yl) propanoate (±)-**3**.* TfOH (15 mg, 0.095 mmol) was added to a stirred

solution of acetate (±)-**11** (1.73 g, 6.35 mmol) in CH_2Cl_2 (64 mL) at room temperature. $NaHCO_3$ (60 mL) was added after 30 min and the mixture was extracted with CH_2Cl_2 (2×50 mL). Combined organic layers were washed with H_2O (2×30 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue (1.5 g) was purified by FLC (75 g SiO_2, hexane/Et_2O with gradient 250:1 to 50:1) to afford pure (±)-*cis*-**3a** (320 mg, 23%), pure (±)-*trans*-**3b** (480 mg, 35%) and mixture of (±)-*cis*/*trans*-**3a**/**b** (400 mg, 30%) as a colourless oils.

*4.2.3.1. (±)-cis-**3a**.* R_f 0.62 (hexanes/EtOAc 6:1); LC–MS: t_R=7.421 min; IR (film on KBr) ν_{max} 3085, 2970–2874 (br), 1735, 1643, 1467, 1431, 1272, 1191, 1145, 1033, 994, 921 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.15, 1.20 (6H, 2×s, CCH_3CH_3), 1.27 (3H, s, CCH_3), 1.68–2.01 (4H, m, CH_2CH_2), 3.67 (3H, s, OCH_3), 4.14–4.24 (1H, m, C*H*), 4.95 (1H, dd, *J* 10.8, 1.5 Hz, CH=CH_aH$_b$); 5.16 (1H, dd, *J* 17.4, 1.5 Hz, CH=CH$_a$$H_b$); 5.92 (1H, dd, *J* 17.4, 10.8 Hz, C*H*=CH$_a$H$_b$); δ_C (75 MHz, $CDCl_3$) 21.0, 21.8, 25.8, 27.2, 37.8, 46.0, 51.9, 82.8, 83.3, 111.3, 144.2, 177.2; HRMS (ESI-TOF): MK^+, calculated for $C_{12}H_{20}O_3K^+$ 251.1044, found 251.1013.

*4.2.3.2. (±)-trans-**3b**.* R_f 0.67 (hexanes/EtOAc 6:1); LC–MS: t_R=8.472 min; IR (film on KBr) ν_{max} 3087, 2974–2875 (br), 1736, 1641, 1471, 1434, 1272, 1191, 1144, 1033, 993, 923, 895 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.14, 1.20 (6H, 2×s, CCH_3CH_3), 1.26 (3H, s, CCH_3), 1.55–1.92 (4H, m, CH_2CH_2), 3.67 (3H, s, OCH_3), 4.09–4.20 (1H, m, C*H*), 4.97 (1H, dd, *J* 10.6, 1.6 Hz, CH=CH_aH$_b$), 5.17 (1H, dd, *J* 17.3, 1.6 Hz, CH=CH$_a$$H_b$), 5.83 (1H, dd, *J* 17.3, 10.6 Hz, C*H*=CH$_a$H$_b$); δ_C (75 MHz, $CDCl_3$) 20.9, 21.5, 26.8, 26.9, 37.3, 46.0, 51.8, 83.0, 83.4, 111.3, 143.7, 177.3; HRMS (ESI-TOF): MH^+, calculated for $C_{12}H_{21}O_3^+$ 213.1485, found 213.1428.

*4.2.4. 2-Methyl-2-(5′-methyl-5′-vinyltetrahydrofuran-2′-yl)propanol (±)-**5**.* LAH (274 mg, 7.2 mmol) was added in few portions to methylester (±)-**3** (765 mg, 3.6 mmol) in Et_2O (36 mL) at 0 °C and the mixture was stirred for 30 min. Next, $Na_2SO_4{\cdot}10H_2O$ (7.55 g, 23.42 mmol) was added and the mixture was stirred overnight at rt. The suspension was filtered through short pad of silica gel (2 cm), washed with Et_2O (3×20 mL) and concentrated under reduced pressure to afford alcohol (±)-**5** (656 mg, 99%) as a colourless oil.

*4.2.4.1. (±)-cis-**5a**.* R_f 0.21 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 3438, 3087, 2966–2871 (br), 1643, 1473, 1368, 1290, 1173, 1121, 1093, 1030–993 (br), 916, 845 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.83, 0.91 (6H, 2×s, CCH_3CH_3), 1.28 (3H, s, CCH_3), 1.65–1.91 (4H, m, CH_2CH_2), 3.27 (1H, br s, CH$_2$O*H*), 3.37–3.52 (2H, m, CH_2OH), 3.83–3.94 (1H, m, C*H*), 4.96 (1H, dd, *J* 10.8, 1.2 Hz, CH=CH_aH$_b$), 5.15 (1H, dd, *J* 17.4, 1.2 Hz, CH=CH$_a$$H_b$), 5.91 (1H, dd, *J* 17.4, 10.8 Hz, C*H*=CH$_a$H$_b$); δ_C (75 MHz, $CDCl_3$) 18.5, 22.7, 26.9, 27.1, 36.8, 37.4, 72.75, 83.3, 87.3, 111.4, 143.6; HRMS (ESI-TOF): MNa^+, calculated for $C_{11}H_{20}O_2Na^+$ 207.1361, found 207.1307.

*4.2.4.2. (±)-trans-**5b**.* R_f 0.24 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 3438, 3087, 2967–2871, 1641, 1472, 1368, 1182, 1129, 1096, 1041–993, 919 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.87, 0.91 (6H, 2×s, CCH_3CH_3), 1.30 (3H, s, CCH_3), 1.62–1.95 (4H, m, CH_2CH_2), 3.37–3.44 (1H, m, CH$_2$O*H*), 3.45–3.51 (2H, m, CH_2OH), 3.82–3.90 (1H, m, C*H*), 4.99 (1H, dd, *J* 10.6, 1.5 Hz, CH=CH_aH$_b$), 5.17 (1H, dd, *J* 17.3, 1.5 Hz, CH=CH$_a$$H_b$), 5.85 (1H, dd, *J* 17.3, 10.6 Hz, C*H*=CH$_a$H$_b$); δ_C (75 MHz, $CDCl_3$) 18.4, 22.7, 26.0, 27.1, 37.4, 37.5, 72.9, 83.0, 86.9, 111.6, 144.1; HRMS (ESI-TOF): MNa^+, calculated for $C_{11}H_{20}O_2Na^+$ 207.1361, found 207.1304.

*4.2.5. 2-Methyl-2-(5′-methyl-5′-vinyltetrahydrofuran-2′-yl)propyl propionate (±)-**4**.* Catalytic amount of DMAP (3 mg) was added to a stirred solution of alcohol (±)-**5** (100 mg, 0.543 mmol), propionic anhydride (182 mg, 1.357 mmol) and Et_3N (192 mg, 1.899 mmol) in CH_2Cl_2 (11 mL) at 0 °C. The cooling bath was removed after 15 min and the reaction mixture was stirred for another 105 min. Water (15 mL) was added and the mixture was extracted with CH_2Cl_2 (2×15 mL). Combined organic layers were washed with saturated aq $CuSO_4$ (25 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue (160 mg) was purified by FLC (4.5 g SiO_2, hexanes/Et_2O 20:1) to afford ester (±)-**4** (105 mg, 80%) as a colourless oil.

*4.2.5.1. (±)-cis-**4a**.* R_f 0.50 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 3086, 2970–2875 (br), 1736, 1643, 1464, 1367, 1177, 1083, 1062, 1019, 993, 917 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88, 0.92 (6H, 2×s, CCH_3CH_3), 1.14 (3H, t, *J* 7.6 Hz, CH$_2$CH_3), 1.26 (3H, s, CCH_3), 1.66–1.90 (4H, m, CH_2CH_2), 2.33 (2H, q, *J* 7.6 Hz, CH_2CH$_3$), 3.78–4.01 (3H, m, C*H*+CH_2OCO), 4.94 (1H, dd, *J* 10.8, 1.5 Hz, CH=CH_aH$_b$), 5.16 (1H, dd, *J* 17.4, 1.5 Hz, CH=CH$_a$$H_b$), 5.92 (1H, dd, *J* 17.4, 10.8 Hz, C*H*=CH$_a$H$_b$); δ_C (75 MHz, $CDCl_3$) 9.4, 20.1, 21.3, 26.0, 26.6, 27.9, 37.4, 38.0, 70.8, 82.2, 83.0, 111.1, 144.6, 174.6; HRMS (ESI-TOF): MNa^+, calculated for $C_{14}H_{24}O_3Na^+$ 263.1623, found 263.1601.

*4.2.5.2. (±)-trans-**4b**.* R_f 0.57 (hexanes/EtOAc, 6:1); IR (ATR) ν_{max} 3087, 2970–2877 (br), 1737, 1641, 1464, 1368, 1184, 1083, 1062, 1019, 994, 920, 895 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.88, 0.91 (6H, 2×s, CCH_3CH_3), 1.14 (3H, t, *J* 7.6 Hz, CH$_2$CH_3), 1.25 (3H, s, CCH_3), 1.53–1.91 (4H, m, CH_2CH_2), 2.33 (2H, q, *J* 7.6 Hz, CH_2CH$_3$), 3.8 (1H, t, *J* 7.1 Hz C*H*), 3.88–3.99 (2H, m, CH_2OCO), 4.95 (1H, dd, *J* 10.6, 1.7 Hz, CH=CH_aH$_b$), 5.14 (1H, dd, *J* 17.3, 1.7 Hz, CH=CH$_a$$H_b$), 5.83 (1H, dd, *J* 17.3, 10.6 Hz, C*H*=CH$_a$H$_b$); δ_C (75 MHz, $CDCl_3$) 9.4, 19.7, 21.3, 26.3, 27.0, 27.8, 37.3, 37.4, 70.7, 82.5, 82.9, 111.1, 144.1, 174.6; HRMS (ESI-TOF): MNa^+, calculated for $C_{14}H_{24}O_3Na^+$ 263.1623, found 263.1625.

*4.2.6. 2-Methyl-2-(5′-methyl-5′-vinyltetrahydrofuran-2′-yl)propanal (±)-**2**.* A solution of alcohol (±)-**5** (445 mg, 2.415 mmol) in CH_2Cl_2 (11.5 mL) was added to a stirred suspension of PCC (781 mg, 3.62 mmol) and 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (23 mL) at 0 °C. After stirring for 1 h, the reaction mixture was warmed to room temperature. After 5 h, the reaction mixture was diluted with hexane (50 mL), filtered through silica gel pad (12 g SiO_2) and washed hexanes/Et_2O 20:1. The concentration of filtrate in vacuo gave aldehyde (±)-**2** (350 mg, 80%) as a colourless oil.[31]

*4.2.6.1. (±)-cis-**2a**.* R_f 0.60 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 3087, 2970–2871 (br), 2711, 1724, 1643, 1467, 1404, 1367, 1120, 1091, 1060, 1031, 993, 916 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.06, 1.08 (6H, 2×s, CCH_3CH_3), 1.28 (3H, s, CCH_3), 1.64–2.01 (4H, m, CH_2CH_2), 4.09 (1H, t, *J* 7.2 Hz, C*H*), 4.97 (1H, dd, *J* 10.8, 1.4 Hz, CH=CH_aH$_b$), 5.16 (1H, dd, *J* 17.4, 1.4 Hz, CH=CH$_a$$H_b$), 5.91 (1H, dd, *J* 17.4, 10.8 Hz, C*H*=CH$_a$H$_b$); δ_C (75 MHz, $CDCl_3$) 17.3, 19.5, 25.9, 27.0, 37.5, 49.2, 82.8, 83.0, 111.6, 143.9, 206.5; HRMS (ESI-TOF): MNa^+, calculated for $C_{11}H_{18}O_2Na^+$ 205.1204, found 205.1175.

*4.2.6.2. (±)-trans-**2b**.* R_f 0.64 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 3087, 2971–2871 (br), 2702, 1724, 1641, 1469, 1401, 1369, 1131, 1097, 1058, 1025, 993, 917, 892 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.01–1.10 (6H, 2×s, CCH_3CH_3), 1.28 (3H, s, CCH_3), 1.58–1.99 (4H, m, CH_2CH_2), 3.96–4.09 (1H, m, C*H*), 4.99 (1H, dd, *J* 10.7, 1.5 Hz, CH=CH_aH$_b$), 5.17 (1H, dd, *J* 17.3, 1.5 Hz, CH=CH$_a$$H_b$), 5.84 (1H, dd, *J* 17.3, 10.7 Hz, C*H*=CH$_a$H$_b$), 9.66 (1H, s, C*H*O); δ_C (75 MHz, $CDCl_3$): 17.0, 19.4, 26.7, 26.8, 37.0, 49.2, 82.8, 83.3, 111.5, 143.5, 206.5; HRMS (ESI-TOF): MNa^+, calculated for $C_{11}H_{18}O_2Na^+$ 205.1204, found 205.1158.

*4.2.7. 2-Methyl-2-(5′-methyl-5′-vinyltetrahydrofuran-2′-yl)propanenitrile (±)-**6**.* A solution of aq NH_4OH (26% w/w, 1.5 mL) was added to aldehyde (±)-**2** (120 mg, 0.658 mmol) in THF (2.25 mL) at −10 °C. After stirring for 5 min, solid I_2 (501 mg, 1.975 mmol) was added at

−10 °C. The cooling bath was removed after 105 min and the reaction mixture was stirred for 15 min at rt. The reaction was quenched with saturated aq $Na_2S_2O_3$ (20 mL) and extracted with Et_2O (3×15 mL). Combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue (130 mg) was purified by FLC (6.5 g SiO_2, hexanes/Et_2O 12:1) to afford nitrile (±)-**6** (101 mg, 86%) as a colourless oil.

*4.2.7.1. (±)-cis-**6a**.* R_f 0.52 (hexanes/EtOAc 6:1); IR (film on KBr) ν_{max} 3087, 2977–2875 (br), 2237, 1846, 1645, 1470, 1408, 1393, 1370, 1306, 1292, 1236, 1193, 1159, 1128, 1097, 1066, 1035, 993, 924, 887 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28–1.33 (6H, 2×s, CCH_3, CCH_3CH_3), 1.42 (3H, s, CCH_3CH_3), 1.75–2.18 (4H, m, CH_2CH_2), 3.79 (1H, t, *J* 6.8 Hz, C*H*), 5.03 (1H, dd, *J* 10.8, 1.1 Hz, CH=CH_aH_b), 5.27 (1H, dd, *J* 17.4, 1.1 Hz, CH=CH_aH_b), 6.00 (1H, dd, *J* 17.4, 10.8 Hz, C*H*=CH_aH_b); δ_C (75 MHz, $CDCl_3$) 23.9, 24.0, 25.9, 28.6, 37.6, 37.8, 83.6, 83.7, 112.1, 123.9, 143.6; HRMS (ESI-TOF): MK^+, calculated for $C_{11}H_{17}NOK^+$ 218.0947, found 218.0908.

*4.2.7.2. (±)-trans-**6b**.* R_f 0.56 (hexanes/EtOAc 6:1); IR (film on KBr) ν_{max} 3089, 2978–2876 (br), 2237, 1846, 1641, 1471, 1404, 1392, 1370, 1303, 1244, 1190, 1131, 1097, 1063, 1036, 995, 924, 883 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28 (3H, s, CCH_3), 1.37, 1.42 (6H, 2×s, CCH_3CH_3), 1.80–2.13 (4H, m, CH_2CH_2), 3.70–3.79 (1H, m, C*H*), 5.01 (1H, dd, *J* 10.6, 1.4 Hz, CH=CH_aH_b), 5.17 (1H, dd, *J* 17.3, 1.4 Hz, CH=CH_aH_b), 5.85 (1H, dd, *J* 17.3, 10.6 Hz, C*H*=CH_aH_b); δ_C (75 MHz, $CDCl_3$): 23.7, 23.9, 26.8, 28.3, 36.8, 37.8, 83.6, 84.1, 111.7, 124.0, 143.4; HRMS (ESI-TOF): MNa^+, calculated for $C_{11}H_{17}NONa^+$ 202.1208, found 202.1164.

*4.2.8. 2-Methyl-5-(2′-methylbut-3′-en-2′-yl)-2-vinyltetrahydrofuran (±)-**7**.* BuLi (0.53 mL, 1.168 mmol, 2.2 M in hexanes) was added to a suspension of methyltriphenylphosphine bromide (439 mg, 1.229 mmol) in dry THF (4 mL) at 0 °C. After stirring for 30 min, aldehyde (±)-**2** (112 mg, 0.615 mmol) in dry THF (0.2 mL) was added at 0 °C. The reaction was quenched with 10% aq HCl (5 mL) and extracted with Et_2O (3×10 mL). Organic layers were washed with H_2O (15 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FLC to afford compound (±)-**7** (77 mg, 70%) as a yellow oil.

*4.2.8.1. (±)-cis-**7a**.* R_f 0.57 (hexanes/EtOAc 12:1); IR (ATR) ν_{max} 3053, 2957–2926 (br), 1645, 1585, 1479, 1464, 1433, 1377, 1304, 1097, 1027, 878, 739, 695, 505, 418 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.00, 1.03 (6H, 2×s, CCH_3CH_3), 1.27 (3H, s, CCH_3), 1.62–1.88 (4H, m, CH_2CH_2), 3.79 (1H, t, *J* 7.0 Hz, C*H*), 4.91–5.23 (4H, m, 2×CH=CH_aH_b), 5.85–6.01 (2H, m, 2×C*H*=CH_aH_b); δ_C (75 MHz, $CDCl_3$) 23.4, 23.7, 25.8, 27.2, 38.0, 40.4, 82.5, 85.9, 111.2, 111.9, 144.6, 145.5; HRMS (ESI-TOF): MNa^+, calculated for $C_{12}H_{20}ONa^+$ 203.1412, found 203.1366.

*4.2.8.2. (±)-trans-**7b**.* R_f 0.60 (hexanes/EtOAc 12:1); IR (ATR) ν_{max} 3055, 2958–2870 (br), 1641, 1585, 1464, 1433, 1379, 1367, 1099, 1027, 920, 878, 738, 694, 505, 478, 420 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.99, 1.03 (6H, 2×s, CCH_3CH_3), 1.28 (3H, s, CCH_3), 1.58–1.70 (2H, m, CH_2), 1.74–1.85 (2H, m, CH_2), 3.73 (1H, t, *J* 7.0 Hz, C*H*), 4.95–5.20 (4H, m, 2×CH=CH_aH_b), 5.79–5.97 (2H, m, 2×C*H*=CH_aH_b); δ_C (75 MHz, $CDCl_3$) 23.3, 23.7, 26.8, 27.0, 37.4, 40.3, 82.7, 86.2, 111.2, 111.9, 144.3, 145.5; HRMS (ESI-TOF): MNa^+, calculated for $C_{12}H_{20}ONa^+$ 203.1412, found 203.1358.

*4.2.9. (E)-Ethyl 6-acetoxy-6-methylocta-2,7-dienoate (±)-**16**.* To a solution of 3-methyl-6-oxohex-1-en-3-yl acetate[26] (±)-**17** (1.605 g, 9.43 mmol) in DCM (31.4 mL) was added methyl (triphenylphosphoranylidene)acetate (3.94 g, 11.32 mmol). The resulting solution was stirred for 1 h at rt, then concentrated under reduced pressure. The residue was diluted with pentane/diethylether (5:1, 25 mL). The formed precipitate was filtered and the filtrate concentrated in vacuo. The oily residue was purified by FLC (47 g SiO_2, pentane/Et_2O 10:1) to afford diester (±)-**16** (1.17 g, 52%) as a colourless oil; R_f=0.47 (6:1, hexanes/EtOAc); IR (ATR) ν_{max} 2981, 2937, 1717, 1654, 1448, 1414, 1367, 1233, 1174, 1098, 1041, 1018, 989, 924, 862, 712, 609 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.54 (3H, s, CCH_3), 1.77–2.09 (5H, m, $OCOCH_3$+CCH_2CH_2), 2.14–2.29 (2H, m, CH_2CH=), 4.17 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.06–5.24 (2H, m, CH_aH_b=CH), 5.81 (1H, dt, *J* 15.6, 1.6 Hz, CH=C*H*COOEt), 5.93 (1H, dd, *J* 17.5, 11.0 Hz, C*H*=CH_aH_b), 6.94 (1H, dt, *J* 15.6, 6.8 Hz, C*H*=CHCOOEt); δ_C (75 MHz, $CDCl_3$) 14.4, 22.2, 23.8, 26.7, 38.1, 60.3, 82.4, 113.8, 121.6, 141.3, 148.5, 166.7, 170.0; HRMS (ESI-TOF): MH^+, calculated for $C_{13}H_{21}O_4^+$ 241.1440, found 241.1434.

*4.2.10. Ethyl 2-(5′-methyl-5′-vinyltetrahydrofuran-2-yl)acetate (±)-**8**.* Diester (±)-**16** (1.01 g, 4.2 mmol) was added to a stirred solution of EtONa (0.315 g, 4.62 mmol) in anhydrous EtOH (21 mL) at 0 °C. The cooling bath was removed after 15 min and the reaction mixture was stirred for another 3 h at rt. The base scavenger[32] G-40 (silica gel supported H_2SO_4, 0.63 g) was added, suspension was filtered through short pad of silica gel and concentrated under reduced pressure. The residue was purified by FLC (40 g SiO_2, pentane/Et_2O with gradient 50:1 to 10:1) to afford (±)-*cis*-**8a** (165 mg, 20%), (±)-*trans*-**8b** (183 mg, 22%) and mixture of (±)-*cis*/*trans*-**8a**/**8b** (100 mg, 12%) as colourless oils.

*4.2.10.1. (±)-cis-**8a**.* R_f 0.48 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 2979, 2934, 2879, 1733, 1639, 1445, 1368, 1300, 1249, 1204, 1175, 1096, 1029, 994, 921, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.30 (3H, s, CCH_3), 1.58–2.11 (4H, m, CH_2CH_2), 2.57 (ddd, *J* 71.9, 15.1, 6.7 Hz, CH_2COOEt), 4.15 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.37–4.49 (1H, m, C*H*), 4.98 (1H, dd, *J* 10.7, 1.6 Hz, CH=CH_aH_b), 5.21 (1H, dd, *J* 17.2, 1.6 Hz, CH=CH_aH_b), 5.91 (1H, dd, *J* 17.2, 10.7 Hz, C*H*=CH_aH_b); δ_C (75 MHz, $CDCl_3$): 14.3, 26.7, 31.6, 37.9, 41.3, 60.5, 75.6, 83.2, 111.7, 144.7, 171.4; HRMS (ESI-TOF): MH^+, calculated for $C_{11}H_{19}O_3^+$ 199.1334, found 199.1324.

*4.2.10.2. (±)-trans-**8b**.* R_f 0.52 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 3087, 2974, 1733, 1643, 1446, 1369, 1300, 1176, 1097, 1029, 994, 920, 881, 849, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.32 (3H, s, CCH_3), 1.64–2.18 (4H, m, CH_2CH_2), 2.56 (ddd, *J* 62.5, 15.1, 6.7 Hz, CH_2COOEt), 4.15 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.31–4.42 (1H, m, C*H*), 4.99 (1H, dd, *J* 10.6, 1.5 Hz, CH=CH_aH_b), 5.20 (1H, dd, *J* 17.2, 1.5 Hz, CH=CH_aH_b), 5.85 (1H, dd, *J* 17.2, 10.6 Hz, C*H*=CH_aH_b); δ_C (75 MHz, $CDCl_3$) 14.3, 27.4, 31.2, 36.9, 41.5, 60.5, 75.1, 83.2, 111.6, 143.7, 171.4; HRMS (ESI-TOF): MH^+, calculated for $C_{11}H_{19}O_3^+$ 199.1334, found 199.1326.

*4.2.11. 2-(5′-Methyl-5′-vinyltetrahydrofuran-2′-yl)ethanol (±)-**9**.* LAH (62 mg, 1.614 mmol) was added in few portions to the solution of (±)-**8** (160 mg, 0.807 mmol) in anhydrous Et_2O (8.1 mL) at 0 °C and the mixture was stirred for 30 min. Then, solid $Na_2SO_4 \cdot 10H_2O$ (1.69 g, 5.25 mmol) was added at once and the resulting suspension was stirred at rt overnight. Next, the suspension was filtered through a short pad of silica gel, washed with Et_2O (3×10 mL) and filtrate was concentrated under reduced pressure. The oily residue was purified by FLC (4 g SiO_2, hexanes/Et_2O 3:1) to afford alcohol (±)-**9** (112 mg, 89%) as a colourless oil.

*4.2.11.1. (±)-cis-**9a**.* R_f 0.34 (hexanes/EtOAc 2:1); IR (ATR) ν_{max} 3390, 3089, 2965, 2931, 2869, 1643, 1444, 1402, 1368, 1288, 1255, 1182, 1125, 1099, 1054, 993, 917, 883, 790, 749, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (3H, s, CCH_3), 1.55-2.07 (6H, m, CH_2CH_2,

CH_2CH_2OH), 2.96 (1H, br s, CH_2OH), 3.80 (2H, m, CH_2OH), 4.14–4.25 (1H, m, C*H*), 4.99 (1H, dd, *J* 10.7, 1.5 Hz, CH=CH_aH_b), 5.21 (1H, dd, *J* 17.3, 1.5 Hz, CH=CH_aH_b), 5.91 (1H, dd, *J* 17.3, 10.7 Hz, C*H*=CH_aH_b); δ_C (75 MHz, $CDCl_3$) 26.7, 32.1, 37.8, 38.4, 61.9, 79.6, 83.5, 111.8, 144.6; HRMS (ESI-TOF): MNa^+, calculated for $C_9H_{16}O_2Na^+$ 179.1048, found 179.1043.

*4.2.11.2. (±)-trans-**9b**.* R_f 0.34 (hexanes/EtOAc 2:1); IR (ATR) ν_{max} 3390, 3087, 2968, 2929, 2871, 1641, 1446, 1402, 1369, 1240, 1127, 1053, 993, 919, 879, 733, 689 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.33 (3H, s, CCH_3), 1.60-2.10 (6H, m, CH_2CH_2, CH_2CH_2OH), 3.04 (1H, br s, CH_2OH), 3.80 (2H, dd, *J* 10.3, 5.1 Hz, CH_2OH), 4.12–4.24 (1H, m, C*H*), 4.99 (1H, dd, *J* 10.6, 1.5 Hz, CH=CH_aH_b), 5.17 (1H, dd, *J* 17.3, 1.5 Hz, CH=CH_aH_b), 5.85 (1H, dd, *J* 17.3, 10.6 Hz, C*H*=CH_aH_b); δ_C (75 MHz, $CDCl_3$): 27.5, 31.7, 36.9, 38.1, 61.8, 79.4, 83.6, 111.5, 143.7; HRMS (ESI-TOF): MH^+, calculated for $C_9H_{17}O_2^+$ 157.1229, found 157.1222.

*4.2.12. 2-(5′-Methyl-5′-vinyltetrahydrofuran-2′-yl)ethanal (±)-**10**.* A solution of alcohol (±)-**9** (77 mg, 0.493 mmol) in DCM (2 mL) was added to a suspension of PCC (159 mg, 0.739 mmol) and 4 Å molecular sieves (0.1 g) in DCM (5 mL) at 0 °C. After stirring for 1 h, the reaction mixture was warmed to rt. and left to stir overnight. The suspension was diluted with hexane (12 mL) and filtered through short pad of silica gel (4 g SiO_2). The solids were washed with hexanes/Et_2O (10:1) and filtrate was concentrated under reduced pressure to furnish partially epimerised aldehyde (±)-**10** (55 mg, 72%) as colourless oil.

*4.2.12.1. (±)-cis-**10a**.* R_f 0.36 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 2968, 2927, 2871, 2727, 1723, 1643, 1448, 1404, 1369, 1290, 1125, 1099, 1072, 1038, 994, 919, 885, 733, 692, 525 cm^{-1}; δ_C (75 MHz, $CDCl_3$) 26.7, 31.9, 37.9, 50.2, 74.1, 83.4, 111.8, 144.5, 201.4; HRMS (ESI-TOF): MH^+, calculated for $C_9H_{15}O_2^+$ 155.1072, found 155.1063.

*4.2.12.2. (±)-trans-**10b**.* R_f 0.38 (hexanes/EtOAc 6:1); IR (ATR) ν_{max} 2970, 2727, 1723, 1641, 1448, 1290, 1126, 1099, 1037, 993, 920, 881, 748, 692 cm^{-1}; δ_C (75 MHz, $CDCl_3$) 27.4, 31.5, 36.9, 50.3, 73.7, 83.5, 111.7, 143.5, 201.5; HRMS (ESI-TOF): MH^+, calculated for $C_9H_{15}O_2^+$ 155.1072, found 155.1064.

*4.2.12.3. (±)-cis/trans-**10a**/**10b**.* δ_H (300 MHz, $CDCl_3$) 1.30–1.35 (3H, m, CCH_3), 1.58–2.22 (4H, m, CH_2CH_2), 2.53–2.80 (2H, m, CH_2CHO), 4.38–4.56 (1H, m, C*H*), 4.96–5.06 (1H, m, CH=CH_aH_b), 5.13–5.25 (1H, m, CH=CH_aH_b), 5.85 (1H, dd, *J* 17.2, 10.6 Hz, C*H*=CH_aH_b for (±)-*trans*-**10b**), 5.91 (1H, dd, *J* 17.2, 10.6 Hz, C*H*=CH_aH_b (±)-*cis*-**10a**), 9.82 (1H, m, C*H*O).

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