## An Expedient Synthesis of Olfactory Lactones by Intramolecular Hydroacylalkoxylation Reactions

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A series of 4,5-disubstituted  $\gamma$ -lactones, including whisky and cognac lactones, was synthesised in four steps from a readily available chiral precursor. By using an intramolecular hydroacylalkoxylation reaction in the final step, a correlation

Introduction

Lactones are ubiquitous in nature as perfumes and pheromones, and are important for the production of flavours, fragrances and agrochemicals.<sup>[1]</sup> Olfactory properties of these compounds are highly dependent upon substituents present, and their relative and absolute stereochemistries on the O-heterocycle. This is exemplified by a class of 4,5-disubstituted  $\gamma$ -lactones, which are key ingredients of whisky, cognac and brandy (Figure 1). The family of lactones comprises four diastereomers, all of which contain a methyl substituent with the (*S*) configuration at the  $\beta$ -position. Differences in their sensory properties are due entirely to substitution at the  $\alpha$ -carbon atom (C-5); whereas the odour of whisky and oak is associated with an *n*-butyl substituent, its *n*-pentyl homologue evokes the aroma of cognac.



Figure 1. cis- and trans-4,5-disubstituted y-lactones.

Perhaps unsurprisingly, the asymmetric synthesis of these lactones is an attractive endeavour, for which there has been a number of reports.<sup>[2]</sup> By excluding methods that rely on the kinetic resolution of racemates or a precursor derived from the chiral pool, the shortest enantioselective route reported for the synthesis of a *trans*-(whisky) lactone so far

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between the (E)/(Z) configuration of the precursor and the product distribution has been established, for the first time, in this type of cyclisation reactions.

involves seven steps from commercially available achiral precursors.<sup>[2f]</sup>

Previously, we have reported the application of Cu-(OTf)<sub>2</sub> for the general addition of an O–H to a C=C bond,<sup>[3]</sup> including intramolecular cyclization of 3-alkenoic acids and 3-alkenols.<sup>[4]</sup> In this work, we examine whether it is possible to extend the methodology to an expedient synthesis of 4,5-disubstituted lactones from  $\alpha$ -methyl- $\gamma$ -butyrolactone (1), which is readily accessible in both enantiomeric forms in high optical purity from cheap, achiral precursors such as 2-methylbutenolide,<sup>[5]</sup> 2-methylene- $\gamma$ -lactone<sup>[6]</sup> or 2methylenesuccinate,<sup>[7]</sup> by well-established bio- and chemocatalytic routes (Scheme 1).



Scheme 1. Stereodivergent synthesis of 3,4-disubstituted  $\gamma$ -lactones.

#### **Results and Discussion**

### Synthesis of Acyclic Precursors

To demonstrate the feasibility of our proposed route, commercially available  $\alpha$ -methyl- $\gamma$ -butyrolactone (±)-1 was employed as the precursor in this work (Scheme 2). Reduction to the lactol 2 was achieved in high yield (92%) by

using DIBAL-H. Conversion to  $\delta$ -alkenols **3a–d** was then accomplished selectively by a Wittig reaction between **2** and an appropriate P-ylide. The (*Z*) isomer predominated in all cases, which can be isolated with yields between 71 and 92%.



Scheme 2. Three-step synthesis of acyclic precursors.

Oxidation of the primary alcohols 3 to their corresponding carboxylic acids 4 proved to be problematic: stoichiometric oxidants (Jones reagent, PDC, KMnO<sub>4</sub>) delivered capricious reaction mixtures. On the other hand, the alcohol is remarkably inert towards IBX, Dess-Martin, and Parikh-Doering oxidations, where no oxidation was observed, even to the aldehyde. (Oxido)ruthenium catalysts  $\{[RuO_3(OH)_2]^{2-}\!/\!S_2O_8{}^{2-} \text{ and } RuCl_3/NaIO_4\}$  also failed to give clean conversions; under these conditions, the dihydroxylation of the C=C bond was competitive. Eventually, some success was achieved by using TEMPO and a buffered solution of NaClO<sub>2</sub>,<sup>[8]</sup> but the reaction terminated at 50% conversion, even by using excess reagents. The problem was finally solved by replacing the inorganic oxidant by PhI(OAc)<sub>2</sub>,<sup>[9]</sup> whereby full clean conversion to  $\delta$ -alkenoic acids 4a-d can be achieved, with isolated yields of ca. 80%.

#### Intramolecular Hydroacyalkoxylation Reactions

Simple Brønsted acids (such as  $H_2SO_4$ ) and superacids (e.g. TfOH<sup>[10]</sup>) can be effective for certain intramolecular cyclizations of alkenoic acids, and have been used for the synthesis of olfactory  $\gamma$ -lactones.<sup>[11]</sup> However, applications are limited by their corrosive nature, which is aggravated by high temperatures needed for these reactions. The low thermal stability of  $H_2SO_4$  can impart an unpleasant odour to the final product by its decomposition to  $SO_2$ . In recent years, there is growing interest in the use of "Lewis super acids" for the synthesis of fragrance materials.<sup>[12]</sup> For example, Al(OTf)<sub>3</sub> has been shown to be an effective catalyst for the cyclisation of unsaturated carboxylic acids to lactones at a temperature of > 100 °C,<sup>[13]</sup> whereas we and others reported the use of Cu(OTf)<sub>2</sub><sup>[4]</sup> and AgOTf<sup>[14]</sup> under milder conditions (83 °C).

Rather interestingly, the cyclisation of 3,5-disubstituted alkenoic acids, such as **4**, was never examined in any of these reports. In terms of "prior art", there was only one related example of a 3-phenyl-4-pentenoic acid substrate 5, which cyclised to form the  $\gamma$ -lactone regioselectively in the presence of either AgOTf or Cu(OTf)<sub>2</sub>, to give a mixture of *cis* and *trans* isomers (Scheme 3).<sup>[4,14]</sup> Thus, the present study will provide an opportunity to assess the selectivity and general applicability of the hydroacyalkoxylation reaction for the synthesis of 4,5-disubstituted  $\gamma$ -lactones. Particularly, the (*E*)/(*Z*) geometry of the acyclic precursor on the resultant product distribution will be a point of interest.



Scheme 3. The only previous example of the cyclisation of a 3-substituted alkenoic acid substrate.

In light of literature precedence, catalytic performances of a strong Brønsted and a Lewis acid were compared in this work: Hence, solutions of  $\delta$ -alkenoic acids (*Z*)-4a–c were refluxed in dichloroethane in the presence of either TfOH (10 mol-%) or Cu(OTf)<sub>2</sub> (5 mol-%) (Scheme 4 and Table 1). In all cases, reactions proceeded with complete conversion, to furnish mixtures of  $\gamma$ - and  $\delta$ -lactone products, 7 and 8, respectively, in an approximately 2:1 ratio. In contrast, the cyclisation of 4d (which would have afforded the insect pheromone eldanolide<sup>[15]</sup>) gave an intractable mixture of products under these conditions.



Scheme 4. Catalysed cyclization of  $\gamma$ -alkenoic acids.

Table 1. Catalyased cyclization of γ-alkenoic acids.<sup>[a]</sup>

	-	-				
Entry	$\mathbb{R}^1$	[cat]	<i>t</i> [h]	Ratio 7/8	5-exo <sup>[b]</sup> (7) cis/trans	6- <i>endo</i> <sup>[c]</sup> ( <b>8</b> ) (mixture)
1	<i>n</i> Pr ( <b>4a</b> )	TfOH	18	63:37	8:92	40:60
2	<i>n</i> Pr ( <b>4a</b> )	Cu(OTf) <sub>2</sub>	90	65:35	11:89	45:55
3	<i>n</i> Bu ( <b>4b</b> )	TfOH	18	64:36	9:91	50:50
4	<i>n</i> Bu ( <b>4b</b> )	Cu(OTf) <sub>2</sub>	42	57:43	12:88	50:50
5	nPent (4c)	TfOH	18	65:35	19:81	36:64
6	nPent (4c)	Cu(OTf) <sub>2</sub>	24	61:39	11:89	46:54
7	<i>n</i> Bu ( <b>4b</b> )	TfOH	1.2	58:42	10:90	40:60

[a] See Exp. Sect. for typical reaction conditions. Reactions of Entries 1–6 were performed with conventional heating (83 °C), whereas reaction of Entry 7 was performed under microwave irradiation. Reactions proceeded with complete conversion to products 7 and 8 in all cases (no side product was observed). Product distribution calculated by integration of <sup>1</sup>H NMR spectrum (see Supporting Information). [b] Calculated by <sup>1</sup>H NMR integration. [c] Relative stereochemistry of *cis/trans* isomers of 8 cannot be assigned as they were inseparable.

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The major isomer of the  $\gamma$ -lactone 7 can be isolated cleanly by column chromatography. The structure of 7c was confirmed by comparison of its NMR spectrum with that reported previously,<sup>[16]</sup> whereas the stereochemical assignment of 7a and 7b was established by NOE experiments (see Supporting Information). In all cases, the selectivity for the *trans* isomer is higher than that previously observed for the cyclisation of 5 (Scheme 3), with ratios ranging from 1:4.3 (Table 1, Entry 5), up to 1:11.5 (Entry 1). In comparison,  $\delta$ -lactones 8a–c, also known to have unique olfactory properties,<sup>[17]</sup> were obtained as an inseparable mixture of *cis* and *trans* isomers with ratios between 1:1 and 1:2. Their identity was established by LC-MS and comparison with literature data.

Reactions can be further accelerated by the application of microwave irradiation, with a small effect on the selectivity (Table 1, Entry 7 vs. Entry 3). Interestingly, for Cu- $(OTf)_2$ -catalysed reactions, faster conversion was observed with increasing chain length – reaching 54, 83 and 96% in 18 h, for the cyclisation of **4a**, **4b** and **4c**, respectively.

The cyclisation of these (*Z*)-alkenoic acids is considerably slower and less regioselective than terminal or (*E*)-alkenoic acids studied in our earlier work [where 5-*exo* products were obtained exclusively by using 2 mol-% of Cu-(OTf)<sub>2</sub> as catalyst<sup>[4]</sup>]. Also in contrast to the earlier study, triflic acid is a more effective catalyst than Cu(OTf)<sub>2</sub> (Table 1, Entries 1, 3 and 5 vs. Entries 2, 4 and 6). It is interesting to note that very similar product distributions were obtained, supporting our earlier idea that TfOH may very well be the active catalyst in both cases.<sup>[4]</sup>

From a synthetic point of view, the intramolecular hydroacylalkoxylation reaction affords *trans*-7 with 50-55% isolated yield. Although this may seem modest, the high yields of the preceding steps, and the short synthetic sequence delivered these olfactory lactones with overall yields between 34 and 38% from 1. This is a very productive route for accessing the homologous series of *trans*-4,5-disubstituted lactones.

#### Mechanistic Insights to the Cyclisation Reaction

Complementary studies were performed in an attempt to improve the selectivity of the process, which provided some interesting insights into the nature of these reactions. First, the reversibility of the process was examined to determine whether the product distribution is the result of a thermodynamic equilibrium. Previously, *cis/trans* isomers of the whisky (oak) lactone have been reported to be stable at 55 °C at pH = 1 for 53 d.<sup>[18]</sup> In the present work, isolated samples of pure trans-7b, as well as a mixture of products depleted of this isomer (trans-7b/cis-7b/cis-8b/trans-8b, in a ratio of 6:38:38:18), were subjected to microwave irradiation in the presence of 10 mol-% TfOH, at 150 °C in DCE for 30 min. As it was previously observed, the lactones are stable even under these harsh conditions; compositions of both solutions, including the isomeric distribution, remained unaffected. Thus, the observed regio- and stereochemistry result from kinetic control during the cyclisation process.

Consequently, cyclisation of different samples of 4c containing varying mixtures of (E) and (Z) isomers were carried out, and the resultant product distributions analysed (Table 2). As was observed before, the formation of *trans*-7c was favoured when Z-4c was used as the precursor, whereas the formation of 8c was unselective (Entries 1 and 2). In contrast, when (E) isomers were present in the starting material, regio- and stereoselectivity for 7c were eroded, whereas the isomeric distribution of the six-membered ring 8c becomes more selective (Entries 3 and 4). Again, the outcome is little affected by the choice of catalyst; thus, they are likely to involve similar intermediates.

Table 2. Product distribution study.<sup>[a]</sup>

		<i>E</i> - and/or Z- <b>4</b>	c [cat] 83 °C → 7c +	- 8c
Entry	<b>4c</b> ( <i>E</i> )/( <i>Z</i> )	[cat]	7c Yield [%] ( <i>cis/trans</i> )	8c Yield [%] (mixture <sup>[b]</sup> )
1	0:100	TfOH	65 (18:82)	35 (50:50)
2	0:100	Cu(OTf) <sub>2</sub>	62 (15:85)	38 (50:50)
3	60:40	TfOH	48 (38:62)	52 (33:67)
4	60:40	Cu(OTf) <sub>2</sub>	44 (40:60)	56 (33:67)

[a] All reactions were complete within 24 h. Reactions proceeded with complete conversion to products 7 and 8 in all cases (no side product was observed). Product distribution calculated by integration of <sup>1</sup>H NMR spectrum. [b] Stereochemistry unassigned.

It is interesting to note that the selectivity of the  $\delta$ -lactone product was enhanced by the presence of the (*E*) isomer. However, this aspect of the reaction was not pursued further at this juncture, as all our attempts to separate and identify the isomers had been unsuccessful.

### Conclusions

During this work, the intramolecular cyclisation of 3,5disubstituted  $\delta$ -alkenoic acids by a hydroacylalkoxylation reaction was examined for the first time. By means of this reaction, an expedient synthesis of 4,5-*trans*-disubstituted olfactory lactones has been developed. By starting from the readily available lactone 1, the desired products were prepared in four steps with an overall yield between 34 and 38%. Given that both optical isomers of 1 are accessible from achiral precursors (Scheme 1), the process offers structural and stereo-diversity for the synthesis of this particular class of disubstituted lactones, which will enable further exploration of their properties.

## **Experimental Section**

**General:** Unless specified, all reagents and catalysts were procured commercially and used as received without purification. Anhydrous solvents were dried by passing through columns of molecular sieves in a solvent purification system. Chemical shifts of NMR spectra are reported in  $\delta$  (ppm), referenced to TMS, and J values are given in Hz. Multiplicities are abbreviated as s (singlet), d (doublet), t



(triplet), q (quartet) and m (multiplet). Infrared spectra were recorded with an FT-IR spectrometer equipped with an ATR accessory.

Tetrahydro-3-methylfuran-2-ol (2):<sup>[19]</sup> A solution of 3-methyldihydrofuran-2(3H)-one (1) (5.0 g, 50 mmol, 1 equiv.) in dry CH<sub>2</sub>Cl<sub>2</sub> (150 mL) was cooled to -78 °C under N2. Diisobutylaluminum hydride (1.0 M in hexanes, 70.3 mL, 70.3 mmol, 1.4 equiv.) was added dropwise to the stirred solution, and the resultant solution was stirred at -78 °C for an additional 5 h. Thereafter, the reaction was quenched by the addition of methanol (48 mL) before the mixture was warmed up to room temperature. The cloudy suspension was then filtered through a pad of Celite, and the residue washed with methanol (30 mL). The combined filtrates were concentrated in vacuo to afford 2 as a colourless oil (4.69 g, 92%). Containing a mixture of cis and trans isomers, this was used in the next step without further purification. IR (liquid film):  $\tilde{v}_{max}$  = 3390 (OH), 1002 (C–O) cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): *cis* isomer:  $\delta$  = 5.25 (d, J = 4.5 Hz, 1 H), 3.76–3.85 (m, 2 H), 2.06–2.16 (m, 1 H), 2.72 (br. s, 1 H), 1.91-2.04 (m, 1 H), 1.66-1.80 (m, 1 H), 1.09 (d, J = 6.8 Hz, 3 H) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 99.1$ , 67.1, 38.5, 30.6,12.8; *trans* isomer:  $\delta = 5.10$  (s, 1 H), 4.00–4.14 (m, 2 H), 3.90-3.99 (m, 1 H), 2.90 (br. s, 1 H), 2.15-2.28 (m, 1 H), 1.46–1.58 (m, 1 H), 1.02 (d, J = 6.8 Hz, 3 H) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 104.2, 66.8, 40.3, 31.6,17.1 ppm. EIMS: m/z (%) = 102 (1) [M<sup>+</sup>], 85 (100), 56 (50), 43 (43).

(Z)-3-Methyloct-4-en-1-ol (3a): A round-bottom flask was charged with *n*-C<sub>4</sub>H<sub>9</sub>PPh<sub>3</sub>Br<sup>[20]</sup> (9.71 g, 24.47 mmol, 2.5 equiv.) and dry THF (80 mL) under  $N_2.$  The suspension was cooled to –42  $^{\circ}\mathrm{C}$  (by using an acetonitrile/dry ice bath), and a solution of *n*BuLi (1.6 M in hexane, 15.33 mL, 2.5 equiv.) was added dropwise. Stirring was maintained at -42 °C until a red solution was generated. Compound 2 (1.0 g, 9.73 mmol, 1 equiv.) was then added slowly by using a syringe pump over 1 h, after which the mixture was warmed up room temperature and stirred overnight. The reaction was quenched by the addition of water (25 mL) and the mixture diluted with EtOAc (25 mL). The aqueous layer was separated and extracted with EtOAc ( $3 \times 50$  mL). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. The crude yellow residue was purified by column chromatography<sup>[21]</sup> to give **Z-3a** (1.08 g, 78%) as a transparent oil.  $R_{\rm f}$  (25% EtOAc/hexane) = 0.5. IR (liquid film):  $\tilde{v}_{max} = 3312$  (br.), 2957, 2929, 2871, 1456, 1376, 1050, 1000, 734 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.35 (dt, J = 11.0, 7.3 Hz, 1 H, =CH), 5.18 (tt, J = 11.0, 1.5 Hz, 1 H,CH=), 3.75–3.55 (m, 2 H, CH<sub>2</sub>O), 2.73–2.56 (m, 1 H, CHMe), 2.13-1.99 (m, 2 H, CH<sub>2</sub>), 1.72-1.57 (m, 2 H, CH<sub>2</sub>), 1.57-1.35 (m, 3 H, CH<sub>2</sub> and OH), 1.00 (d, J = 6.7 Hz, 3 H, CHMe), 0.93 (t, J =7.4 Hz, 3 H, CH<sub>2</sub>Me) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 135.7, 129.1, 61.7, 40.2, 29.5, 28.9, 23.0, 21.5, 13.8 ppm. HRMS (CI, NH<sub>3</sub>): calcd. for C<sub>9</sub>H<sub>22</sub>NO 160.1701; found 160.1702  $[MNH_4]^+$ .

(*Z*)-3-Methylnon-4-en-1-ol (3b): Prepared according to a procedure similar to that described for 3a, from n-C<sub>5</sub>H<sub>11</sub>PPh<sub>3</sub>Br<sup>[20]</sup> (9.99 g, 24.2 mmol, 2.5 equiv.) and 2 (0.99 g, 9.67 mmol, 1 equiv.) The product was purified by column chromatography to yield *Z*-3b (1.24 g, 82%) as a transparent oil.  $R_{\rm f}$  (20% EtOAc/hexane) = 0.45. IR (liquid film):  $\tilde{v}_{\rm max}$  = 3335 (br.), 2957, 2926, 2873, 1456, 1372, 1050, 999, 734 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.34 (dt, *J* = 11.0, 7.3 Hz, 1 H, CH=), 5.15 (tt, *J* = 11.0, 1.5 Hz, 1 H, =CH), 3.75–3.50 (m, 2 H, CH<sub>2</sub>OH), 2.73–2.53 (m, 1 H, CHMe), 2.17–1.94 (m, 2 H, CH<sub>2</sub>), 1.61 (dtd, *J* = 11.9, 6.8, 5.1 Hz, 1 H, CH<sub>a</sub>H<sub>b</sub>), 1.52–1.41 (m, 1 H, CH<sub>a</sub>H<sub>b</sub>), 1.37–1.26 (m, 4 H, 2 CH<sub>2</sub>), 0.97 (d, *J* = 6.7 Hz, 3 H, CH*Me*), 0.90 (t, *J* = 7.0 Hz, 3 H, CH<sub>2</sub>*Me*) ppm. <sup>13</sup>C

NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 135.5, 129.3, 61.7, 40.2, 32.1, 28.8, 27.1, 22.4, 21.6, 14.0 ppm. MS (CI, NH<sub>3</sub>): *m*/*z* = 174 [MNH<sub>4</sub>]<sup>+</sup>.

(*Z*)-3-Methyldec-4-en-1-ol (3c): Prepared according to a procedure similar to that described for 3a, from *n*-C<sub>6</sub>H<sub>13</sub>PPh<sub>3</sub>Br<sup>[22]</sup> (11.62 g, 24.5 mmol, 2.5 equiv.) and 2 (1 g, 9.73 mmol, 1 equiv.). The crude product was purified by column chromatography to yield 3c (1.53 g, 92%) as a colourless oil.  $R_{\rm f}$  (CH<sub>2</sub>Cl<sub>2</sub>) = 0.45. IR (liquid film):  $\tilde{v}_{\rm max}$  = 3332 (br.), 2956, 2925, 1457, 1051, 999, 742 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.34 (dt, *J* = 11.0, 7.3 Hz, 1 H, CH=), 5.16 (tt, *J* = 11.0, 1.5 Hz, 1 H, =CH), 3.71–3.55 (m, 2 H, CH<sub>2</sub>OH), 2.69–2.53 (m, 1 H, CHMe), 2.18–1.93 (m, 2 H, CH<sub>2</sub>), 1.68–1.18 (m, 9 H, 4 CH<sub>2</sub>, OH), 0.98 (d, *J* = 6.8 Hz, 3 H, CH*Me*), 0.89 (t, *J* = 6.8 Hz, 3 H, CH<sub>2</sub>*Me*) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 135.5, 129.4, 61.7, 40.3, 31.5, 29.6, 28.8, 27.4, 22.6, 21.6, 14.1 ppm. HRMS (CI, NH<sub>3</sub>): calcd. for C<sub>11</sub>H<sub>26</sub>NO 188.2014, found 188.2010 [MNH<sub>4</sub>]<sup>+</sup>.

3,7-Dimethylocta-4,6-dien-1-ol (3d): Prepared according to a procedure similar to that described for 3a, from (3-methylbut-2-en-1yl)triphenylphosphonium bromide<sup>[23]</sup> (8 g, 19.47 mmol, 2.5 equiv.) and 2 (0.8 g, 7.78 mmol, 1 equiv.). The crude yellow residue was purified by column chromatography using CH<sub>2</sub>Cl<sub>2</sub> to yield an inseparable mixture of (Z) and (E) isomers (ratio 46:54) as a transparent oil (0.85 g, 71%). IR (liquid film):  $\tilde{v}_{max} = 3378$  (br.), 2970, 2932, 2876, 1695, 1457, 1377, 1150, 1052, 970 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (Z) isomer:  $\delta = 6.15$  (t, 1 H, J = 11.0 Hz, CH=), 6.07 (d, 1 H, J = 11.0 Hz, =CH), 5.11 (t, 1 H, J = 11.0 Hz, =CH), 3.74-3.57 (m, 2 H, CH<sub>2</sub>OH), 2.90-2.74 (m, 1 H, CHMe), 1.82 (s, 3 H, Me), 1.78 (s, 3 H, Me), 1.72-1.38 (m, 2 H, CH<sub>2</sub>), 1.03 (d, 3 H, J = 6.7 Hz, CHMe); (Z) isomer:  $\delta = 6.22$  (dd, 1 H, J =15.1, 10.8 Hz, CH=), 5.77 (d, 1 H, J = 10.8 Hz, =CH) 5.42 (dd, 1 H, J = 15.1, 8.3 Hz, CH=), 3.73–3.55 (2 H, m CH<sub>2</sub>OH), 2.45–2.28 (m, 1 H, CH<sub>2</sub>), 1.82 (s, 3 H, Me), 1.78 (s, 3 H, Me), 1.72-1.38 (m, 2 H, CH<sub>2</sub>), 1.06 (d, 3 H, J = 6.8 Hz, CHMe). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, mixture of isomers):  $\delta$  =137.0, 135.9, 134.9, 133.6, 125.5, 124.9, 124.0, 120.1, 61.5, 61.4, 40.2, 39.9, 34.1, 28.9, 26.4, 25.9, 21.5, 21.1, 18.3, 18.1 ppm. HRMS (CI, NH<sub>3</sub>): calcd. for C<sub>10</sub>H<sub>22</sub>NO 172.1701, found 172.1698 [MNH<sub>4</sub>]<sup>+</sup>.

Typical Procedure for the Oxidation of Alcohols 3 to Acids 4: A mixture of diacetoxyiodobenzene (1.0 g, 3.1 mmol) and the alcohol (1.4 mmol) was suspended in acetonitrile/water (1:1, 6.6 mL). This mixture was sonicated for 3 min until the reagents were completely dissolved. TEMPO (0.044 g, 0.2814 mmol), was then added to the reaction vessel and the reaction mixture was stirred at room temperature for 7 h. After this time, the aqueous layer was extracted with  $Et_2O$  (3×15 mL). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography.

(*Z*)-3-Methyloct-4-enoic Acid (4a): Obtained from 3a (0.20 g, 1.4 mmol). Purified by column chromatography using 10% EtOAc/ hexane, the product was obtained as a transparent oil (180 mg, 82%). IR (liquid film):  $\tilde{v}_{max} = 2961, 2929, 1706, 1411, 1291, 1193, 937, 738 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): <math>\delta = 11.0$  (br. s, 1 H, OH), 5.34 (dt, J = 11.0, 7.4 Hz, 1 H, CH=), 5.21 (tt, J = 11.0, 1.5 Hz, 1 H, =CH), 3.09–2.89 (m, 1 H, CHMe), 2.40–2.19 (m, 2 H, CH<sub>2</sub>), 2.12–1.94 (m, 2 H, CH<sub>2</sub>), 1.48–1.23 (m, 2 H, CH<sub>2</sub>), 1.04 (d, J = 6.7 Hz, 3 H, CHMe), 0.89 (t, J = 7.4 Hz, 3 H, CH<sub>2</sub>Me) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 179.3, 133.5, 129.8, 42.0, 29.4, 28.9, 22.8, 20.9, 13.7$  ppm. HRMS (CI, NH<sub>3</sub>): [MNH<sub>4</sub>]<sup>+</sup>, found 174.1495. C<sub>9</sub>H<sub>20</sub>NO<sub>2</sub> requires 174.1494.

(Z)-3-Methylnon-4-enoic Acid (4b): Prepared by using 3b (100 mg, 0.64 mmol). Purified by column chromatography using 25% EtOAc/hexane; the product was obtained as a transparent oil

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(92 mg, 85%). IR (liquid film):  $\tilde{v}_{max} = 2959, 2928, 1706, 1412, 1290, 929, 747 cm^{-1}$ . <sup>1</sup>H NMR: (400 MHz, CDCl<sub>3</sub>):  $\delta = 11.4$  (br. s, 1 H, OH), 5.34 (dt, J = 11.0, 7.4 Hz, 1 H, CH=), 5.19 (tt, J = 11.0, 1.5 Hz, 1 H, =CH), 3.13–2.93 (m, 1 H, CHMe), 2.43–2.22 (m, 2 H, CH<sub>2</sub>), 2.43–2.02 (m, 2 H, CH<sub>2</sub>), 1.41–1.28 (m, 4 H, 2 CH<sub>2</sub>), 1.07 (d, J = 6.8 Hz, 3 H, CHMe), 0.92 (t, J = 6.8 Hz, 3 H, CH<sub>2</sub>Me) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 179.0, 133.3, 130.1, 41.9, 31.9, 28.9, 27.1, 22.3, 21.0, 14.0 ppm. HRMS (CI, NH<sub>3</sub>): calcd. for C<sub>10</sub>H<sub>22</sub>NO<sub>2</sub> 188.1651, found 188.1653[MNH<sub>4</sub>]<sup>+</sup>.$ 

(*Z*)-3-Methyldec-4-enoic Acid (4c): Prepared from 3c (100 mg, 0.54 mmol). Purified by column chromatography using 25% EtOAc/hexane, which afforded the product as a transparent oil (93 mg, 86%). IR (liquid film):  $\tilde{v}_{max} = 2958$ , 2926, 1706, 1410, 1292, 969 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 5.35$  (dt, J = 11.0, 7.6 Hz, 1 H, CH=), 5.20 (tt, J = 11.0, 1.5 Hz, 1 H, =CH), 3.12–2.94 (m, 1 H, CHMe), 2.41–2.23 (m, 2 H, CH<sub>2</sub>), 2.14–2.03 (m, 2 H, CH<sub>2</sub>), 1.48–1.12 (m, 6 H, 3 CH<sub>2</sub>), 1.12–0.96 (d, J = 6.8 Hz, 3 H, CH*Me*), 0.92 (t, J = 6.8 Hz, 3 H, CH<sub>2</sub>*Me*) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 179.0$ , 133.3, 130.2, 126.9, 41.9, 31.5, 29.4, 27.3, 22.6, 21.0, 14.1 ppm. HRMS (CI, NH<sub>3</sub>): calcd. for C<sub>11</sub>H<sub>24</sub>NO<sub>2</sub> 202.1807, found 202.1804 [MNH<sub>4</sub>]<sup>+</sup>.

(Z)- and (E)-3,7-Dimethylocta-4,6-dienoic Acid (4d): Obtained from **3d** (0.22 g, 1.43 mmol). Purified by column chromatography using 25% EtOAc/hexane to yield a inseparable mixture of (Z) and (E) isomers as a transparent oil (175 mg, 73%). IR (liquid film):  $\tilde{v}_{max}$ = 2966, 2927, 1705, 1410, 1291, 1208, 957, 757 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (Z) isomer:  $\delta = 6.05-6.19$  (m, 2 H, CH=), 5.13 (t, J = 10.0 Hz, 1 H, =CH), 3.24–3.06 (m, 1 H, CHMe), 2.43–2.27 (m, 2 H, CH<sub>2</sub>), 1.79 (s, 3 H, Me), 1.75 (s, 3 H, Me), 1.06 (d, J =6.7 Hz, 3 H, CHMe); (E) isomer:  $\delta = 6.26$  (dd, J = 15.1, 10.0 Hz, 1 H, =CH), 5.78 (d, J = 10.0 Hz, 1 H, CH=), 5.48 (dd, J = 15.1, 7.5 Hz, 1 H, =CH), 2.81–2.63 (m, 1 H, CHMe), 2.47–2.24 (m, 2 H, CH<sub>2</sub>), 1.74 (s, 6 H, 2 Me), 1.09 (d, J = 6.7 Hz, 3 H, CHMe) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>, mixture of isomers):  $\delta$  = 178.8, 136.3, 134.8, 134.3, 132.5, 125.8, 124.7, 124.4, 120.0, 41.8, 41.65, 33.6, 29.0, 26.3, 25.9, 20.85, 20.3, 18.25, 18.1 ppm. MS (TOF, ES):  $m/z = 167 [M - H]^{-}$ .

**General Procedure for Cyclization Reactions:** A Radley's reaction tube was charged with a magnetic stir bar, and a mixture of the requisite (*Z*)-alkenoic acid (1 mmol), copper(II) triflate (0.05 mmol, 5 mol-%) or triflic acid (8.8  $\mu$ L, 0.1 mmol, 10 mol-%) and 1,2-dichloroethane (2 mL) was added. The vessel was fitted with a Teflon screwcap, placed in the reaction carousel and heated at reflux for the required length of time. After cooling, the solvent was removed under reduced pressure to furnish a residue, which was purified by column chromatography (EtOAc/hexane, 1:4). The *trans*-7 isomer always eluted first, followed by *cis*-7<sup>[24–25]</sup> (insufficient quantity for characterisation), and finally a mixture of the *cis/trans*-6 products. Alternatively, these reactions were performed under microwave radiation in DCE at 150 °C by using a Biotage Initiator 2.5 instrument.

(±)-*trans*-3-Methyl-4-octanolide, *trans*-Whisky Lactone (7a):<sup>[26]</sup> Colourless oil. IR (liquid film):  $\tilde{v}_{max} = 2960, 2935, 1773, 1459, 1210, 1171, 983, 926 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): <math>\delta = 4.01$  (dt, J = 7.8, 4.0 Hz, 1 H, CHO), 2.75–2.57 (m, 1 H, CHMe), 2.30–2.13 (m, 2 H, CH<sub>2</sub>), 1.74–1.26 (m, 6 H, 3 CH<sub>2</sub>), 1.13 (d, J = 6.4 Hz, 3 H, CHMe), 0.90 (t, J = 6.7 Hz, 3 H, CH<sub>2</sub>Me) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 176.7, 87.5, 37.2, 36.1, 33.7, 27.9, 22.5, 17.5, 13.9 ppm.$ *m*/z (CI, NH<sub>3</sub>) 174 [MNH<sub>4</sub>]<sup>+</sup>.

(±)-*trans*-3-Methyl-4-nonanolide, *trans*-Cognac Lactone (7b):<sup>[27]</sup> Colourless oil. IR (liquid film):  $\tilde{v}_{max} = 2958$ , 2932, 1778, 1459, 1207, 1169, 1001, 937 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 4.03$  (dt, J = 7.8, 4.0 Hz, 1 H, CHO), 2.77–2.62 (m, 1 H, CHMe), 2.33–2.13 (m, 2 H, CH<sub>2</sub>), 1.77–1.24 (m, 8 H, 4 CH<sub>2</sub>), 1.12 (d, J = 6.4 Hz, 3 H, CH*Me*), 0.89 (t, J = 6.8 Hz, 3 H, CH<sub>2</sub>*Me*) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 176.7$ , 87.5, 37.1, 36.1, 33.99, 31.6, 25.4, 22.5, 17.5, 14.0 ppm. MS (CI, NH<sub>3</sub>): m/z = 188 [MNH<sub>4</sub>]<sup>+</sup>.

(±)-*trans*-5-Hexyl-4-methyldihydrofuran-2(3*H*)-one (7c):<sup>[16]</sup> Colourless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.04 (dt, 1 H, *J* = 7.8, 3.9 Hz, CHO), 2.79–2.62 (m, 1 H, C*H*Me), 2.34–2.13 (m, 2 H, CH<sub>2</sub>), 1.77–1.22 (m, 10 H, 5 CH<sub>2</sub>), 1.13 (d, 3 H, *J* = 6.4 Hz, CH*Me*), 0.91 (t, 3 H, *J* = 6.8 Hz, CH<sub>2</sub>*Me*) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 176.6, 87.5, 37.1, 36.1, 34.0, 31.6, 29.5, 25.7, 22.5, 17.5, 14.0 ppm.

**Supporting Information** (see footnote on the first page of this article): IR and NMR (<sup>1</sup>H and <sup>13</sup>C) spectra of all intermediates and products, an example of how product distribution is determined by <sup>1</sup>H NMR integration, and NOE experiments with *trans*-**7a** and **7b**.

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