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An Efficient and Facile Synthesis of Capsaicin-Like Compounds as Agonists of the TRPV1 Receptor

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A new versatile synthetic route is described for the preparation of capsaicin-like molecules which contain an α-hydroxy ketone functional group mimicking the amide functional group in the capsaicin structure. The key reaction in this synthesis was the formation of α-(dimethylamino)alkanenitriles as intermediates. These nitriles were successfully prepared from both aliphatic and aromatic aldehydes by reaction with dimethylamine and aqueous sodium cyanide. Treatment of the nitriles with lithium diisopropylamide (LDA) followed by reaction with various aldehydes led to the formation of α-hydroxy ketone compounds, examples of which include 2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodecan-3-one, (5*R*)- and (5*S*)-2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-5,9-dimethyldec-8-en-3-one, representing novel capsaicin-like molecules. Formation of (4-benzyloxy-3-methoxyphenyl)-acetaldehyde was also described from the Wittig reaction of 4-benzyloxy-3-methoxybenzadehyde with an ylide reagent (methoxymethyl)triphenylphosphonium bromide followed by acid hydrolysis to form the title compound. This aldehyde represents a useful precursor for the synthesis of capsaicin-like structures.

Introduction

Capsaicin, the main pungent principle in "hot" chilli peppers of the *Capsicum* family, was identified with an initial action to activate the "capsaicin receptor" or vanilloid ion-channel receptor (TRPV1) in the sensory nervous system.[1–4] One well known property of capsaicin is to excite some, but not all, sensory neurones and by doing so, capsaicin evokes an inward depolarizing current which is associated with a conductance increase, and the sensation of "burning".[1,5] Exposure to capsaicin results in activation, followed by desensitization, of lightly myelinated or unmyelinated primary afferent fibers.[2] The latter is believed to account for the antinociceptive effect observed in a number of analgesic models.[6–9]

Structure–activity relationship studies on capsaicin-like compounds have been extensively investigated and have involved modification of three regions of the capsaicin structure: the aromatic region (A region),[10] the amide functional group (B region)[11] and the hydrophobic side chain (C region)[12] (Figure 1). In the amide functional group in particular, the carbonyl and the amino group were either interchanged or replaced with an urea or thiourea group.[11] It was shown that almost all compounds containing amide, "reversed" amide, urea or thiourea functional groups exhibited potent activity in increasing $^{45}Ca^{2+}$ influx in dorsal root ganglion (DRG) neurons.[11] In some cases, compounds with modified structures, particularly the thiourea derivatives, exhibited even more potent activity than capsaicin in increasing $^{45}Ca^{2+}$ influx in DRG neurones.[11]

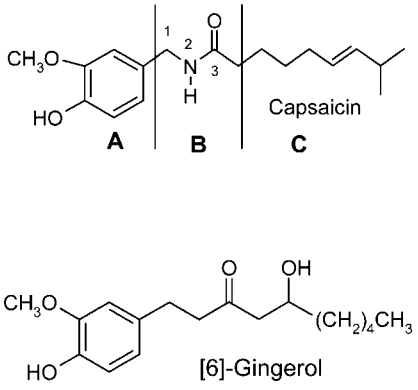

Figure 1. Structures of capsaicin and [6]-gingerol.

We have discovered [6]-gingerol [5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one] (Figure 1), a pungent principle of the rhizome of ginger (*Zingiber officinale*) activates capsaicin-sensitive receptor isolated from dorsal root ganglia of neonatal rats. This activation was abolished by the TRPV1 antagonist capsaizepine.[13] [6]-Gingerol, however, contains a chemically labile β-hydroxy ketone (B region) group, which is prone to dehydration to form [6]-shogaol [1-(4-hydroxy-3-methoxyphenyl)dec-4-en-3-one].[14] Introduction of an α-hydroxy ketone functional group at the B region to replace the amide group in capsaicin, and β-hy-

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droxy ketone group in [8]-gingerol [5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodecan-3-one] not only improves chemical stability of the compound but also retains agonistic activity on the TRPV1 from rat isolated DRG neurons.[15]

We report here the synthesis of a novel class of TRPV1 agonists containing an α-hydroxy ketone functional group, via aldol condensation of an aldehyde with an α-(dimethylamino)alkanenitrile intermediate. The latter is obtained from the reaction of aliphatic or aromatic aldehydes with dimethylamine and aqueous sodium cyanide. This concise and versatile synthetic route allowed us to obtain compounds with the α-hydroxy ketone functional group at C1 (**14**), C2 (**17**, **18** and **19**), or C3 (**16**) on the side chain. Of particular interest is the series of compounds **17**, **18** and **19**, which may be viewed as novel capsaicin analogues in which the amide (NHCO) group is replaced by an α-hydroxy ketone [CH(OH)CO] group. We also report the synthesis of compounds with the "reversed" α-hydroxy ketone functional group (**20** and **22**), where the hydroxy and ketone groups are interchanged in their positions on the side chain compared with the corresponding "parent" compounds **14**, and **16**.

Results and Discussion

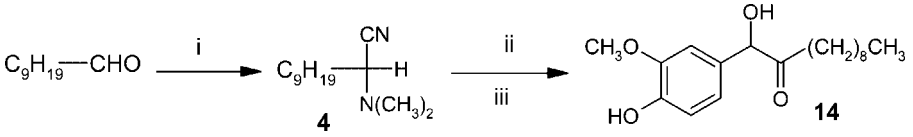
The synthetic routes as described in Scheme 1 and Scheme 2 have resulted in compounds having an α-hydroxy ketone functional group at C1 (**14**), C2 (**17**, **18**, **19**) or C3 (**16**) on the side chain relative to the aromatic moiety as shown in Figure 2. These compounds, particularly **17**, **18** and **19**, represent novel capsaicin hybrid structures in which the α-hydroxy ketone replaced the amide group in the capsaicin molecule (Figure 1). The synthetic route as described in Scheme 1 also allowed for the preparation of the so called "reversed" α-hydroxy ketone compounds **20** and **22**, in which the hydroxy and carbonyl group interchange their position on the side chain compared with the corresponding compounds **14** and **16**, respectively (Figure 2). Structures of the intermediate compounds are shown in Figure 3.

The formation of α-(dimethylamino)alkanenitriles **3**–**6** of aliphatic aldehydes, as shown in step i of Scheme 1, from nonanal, decanal, (3*R*)-3,7-dimethyl-6-octenal and (3*S*)-3,7-dimethyl-6-octenal, and α-(dimethylamino)alkanenitriles **7** and **8** from aromatic aldehydes, including 3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]benzaldehyde (**1**) and 3-{3-methoxy-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]phenyl}-2-propenal (**2**), were achieved essentially in quantitative yield. The nitriles **5** and **6** were prepared from optically pure (*R*)- and (*S*)-3,7-dimethyl-6-octenal enantiomers, respectively, which were commercially available. Lithium derivatives of aromatic α-(dimethylamino)alkanenitriles proved to be more reactive than those of aliphatic α-(dimethylamino)alkanenitriles in the condensation reaction (step ii, Scheme 1; step iv, Scheme 2), which was carried out at a temperature of not higher than –50 °C, as above this temperature polymerisation may occur. Yields were moderate in most cases, and products were readily purified by normal-phase silica gel short-column vacuum chromatography as described in the Exp. Sect.

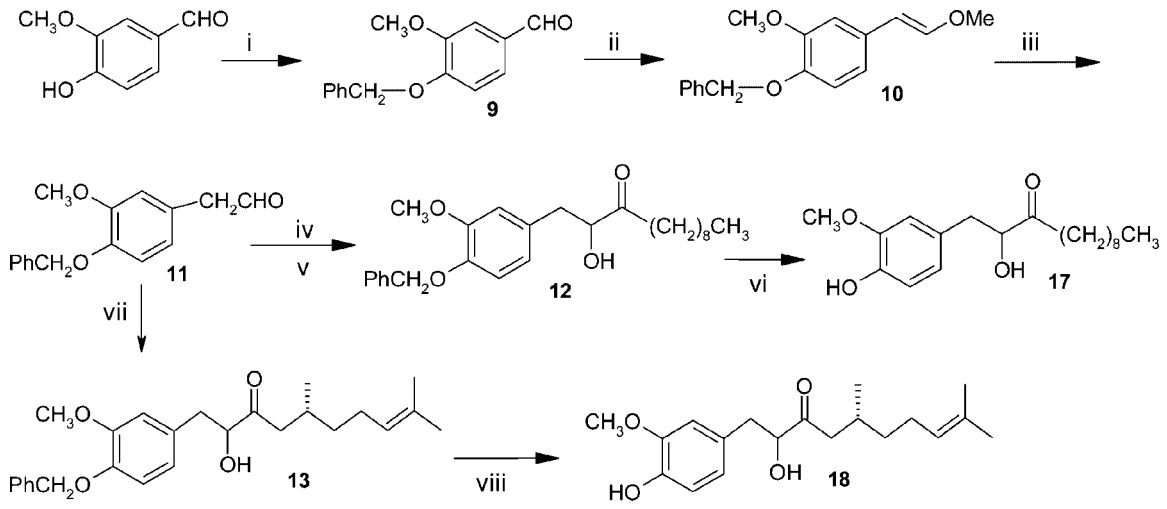
The tetrahydropyran-2-yl (THP) group was used as protecting group in Scheme 1 for its facile removal, which occurred simultaneously with the conversion of the α-(dimethylamino)alkanenitriles to α-hydroxy ketone in aqueous oxalic acid.[16] The THP group was, however, unsuitable for the synthesis of compounds **17**, **18** and **19** according to Scheme 2, because it would be cleaved by acid hydrolysis (step iii, Scheme 2) of **10** to form **11**. In this case a benzyl group, readily removed by catalytic hydrogenation, was used to protect the phenolic OH group.[17]

All synthetic routes described in this study can accommodate compounds with a double bond in the side chain, which can be hydrogenated to produce saturated congeners for structure-activity relationship study. Of particular interest is the synthesis of **18** and **19** (Scheme 2 and Figure 2), which contain a double bond at the methyl end of the side chain, representing similar structure to the capsaicin molecule. The protecting benzyl group was effectively removed by palladium-catalyzed hydrogen transfer in cyclohexene (step viii, Scheme 2).[18]

All aldehydes used in this study are commercially available except for (4-benzyloxy-3-methoxyphenyl)acetaldehyde (**11**), which was obtained by Wittig reaction of 4-benzyloxy-3-methoxybenzaldehyde (i.e. vanillin benzyl ether) with a phosphorus ylide reagent generated from (methoxymethyl)-triphenylphosphonium bromide and potassium *tert*-butoxide, as described in Scheme 2 (step ii). This aldehyde represents a useful precursor for the synthesis of capsaicin hybrid structures in which the nitrogen atom in capsaicin structure is replaced by an alcohol moiety to form an α-hydroxy ketone functional group that mimics the amide group in the capsaicin structure. The synthetic route described for the preparation of α-hydroxy ketones in this study resulted in a racemic mixture, which allows for further isolation of optically pure enantiomers for enantiospecific investigation of the compounds on the TRPV1 receptor.



Scheme 1. Reagents and conditions: (i) aq. $NaHSO_3$, MeOH/H_2O: 9:1, $NH(CH_3)_2$, aq. NaCN, room temp., 16 h, **4**: 94%; (ii) 1.3 equiv. LDA, THF, –80 °C to room temp., 2 h, then 1 equiv. of **1**, –80 °C, 5 h; (iii) aq. oxalic acid, THF, reflux, 1.5 h followed by chromatography **14**: 74%.



Scheme 2. Reagents and conditions: (i) NaH, DMF, $PhCH_2Br$, room temp., 30 min, followed by chromatography, **9**: 92%; (ii) 1 equiv. (methoxymethyl)triphenylphosphonium bromide, 1.5 equiv. potassium *tert*-butoxide, 0 °C, 30 min, followed by chromatography, **10**: 78%; (iii) THF/HCl, reflux, followed by chromatography, **11**: 60%; (iv) 1 equiv. **4** [or (vii) 1 equiv. **5**], 1.3 equiv. LDA, THF, –80 °C to room temp., 2 h, then 1 equiv. **11**, –80 °C, 5 h; (v) aq. oxalic acid, THF, reflux, 1.5 h, followed by chromatography, **12**: 85% or **13**: 78%; (vi) H_2, Pd-C, EtOAc, room temp., 4 h, followed by chromatography, **17**: 92%; (viii) EtOH/cyclohexene: 2:1, Pd-C, reflux, 3 h, followed by chromatography, **18**: 80%.

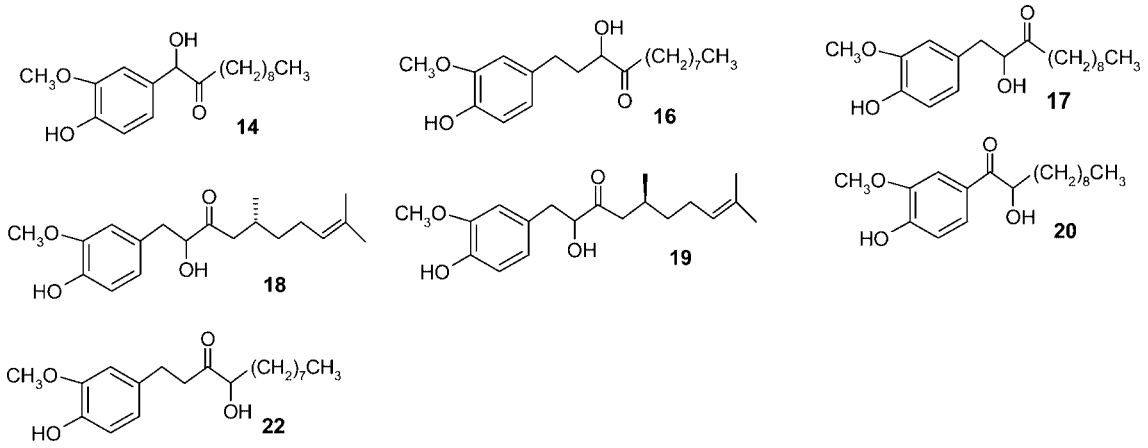


Figure 2. Structures of α-hydroxy ketone compounds.

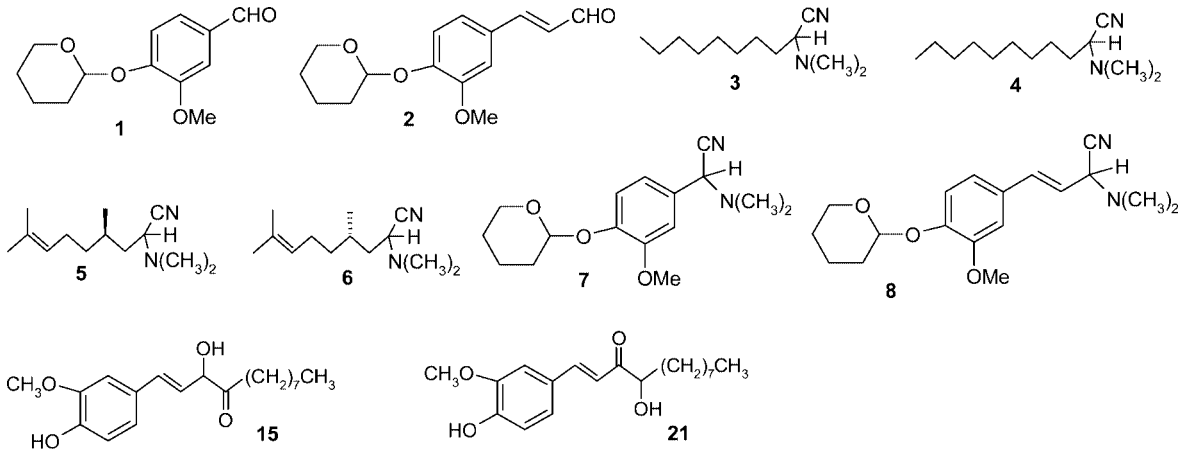


Figure 3. Structures of intermediate compounds.

Preliminary investigation of the α-hydroxy ketones described in this study for activity on the TRPV1 receptor in isolated dorsal root ganglion (DRG) neurons in culture, showed that these compounds, at 10 μM, evoked $[Ca^{2+}]_i$ transients in Fura-2 loaded DRG neurons.[15] The activation of the receptor by these α-hydroxy ketones exclusively occurred in capsaicin-sensitive neurones and was antagonised by capsazepine, a capsaicin receptor antagonist.[15]

The discovery of the series of α-hydroxy ketones as novel TRPV1 agonists was a result of combining structural features of capsaicin and gingerol molecules in the development of TRPV1 agonists. Molecular comparison of the TRPV1 agonists using molecular modelling as described in the Exp. Sect. showed that the molecular structures, particularly regions "A" and "B", superimposed well to one another (Figure 4) indicating that these molecules could act on the same active site on TRPV1. These findings provide a model for further drug design and structure–activity relationship analysis of α-hydroxy ketones as TRPV1 agonists.

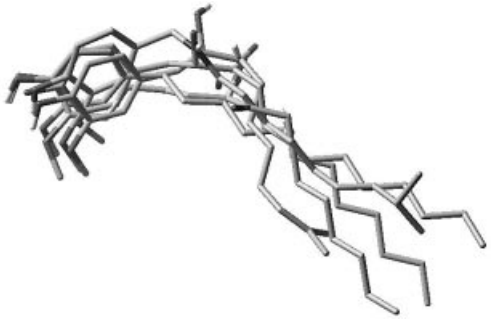


Figure 4. Low-energy conformers of capsaicin, [8]-gingerol and α-hydroxy ketone compounds. The molecules of the TRPV1 agonists were constructed, energy minimisation and superimposed using Maestro version 6.0.107, MM share version 1.2.014, Shrodinger, L.L.C.

Conclusions

In summary, it was demonstrated that α-(dimethylamino)-alkanenitriles, derived from various aldehydes including aliphatic and aromatic aldehydes, are versatile intermediates for the synthesis of α-hydroxy ketone compounds to mimic the amide functional group in the capsaicin molecule. As a result, representative compounds with the α-hydroxy ketone functional group at the C1, C2 or C3 position on the side chain relative to the aromatic moiety were synthesised. The synthetic routes described in this study allowed for the synthesis of the respective α-hydroxy ketones and their "reversed" α-hydroxy ketone congeners for further structure-activity relationship studies on the activation of the TRPV1 receptor in a drug discovery and development program.

Experimental Section

General: Solid compounds were recrystallised from ethyl acetate/*n*-hexane and melting points were taken with a hot stage microscope and are uncorrected. ^1H and ^{13}C spectra were recorded with Varian Gemini 300 BB spectrometer [300 MHz, δ = 0 ppm (TMS), in $CDCl_3$]. Chemical shifts are expressed in ppm (δ relative to TMS as internal reference). *J* values are given in Hz. MS were measured with ThermoFinnigan PolarisQ ion trap MS/MS system by electron impact (EI), or by chemical ionization (CH_4). All experiments sensitive to air and/or to moisture were carried out under nitrogen. Analytical thin-layer chromatography (TLC) was performed on silica gel pre-coated TLC plates (Merck, 60, F254). Chromatographic purification was carried out by short-column vacuum chromatography using Merck silica gel (60 H). Anhydrous tetrahydrofuran (THF) was freshly distilled from sodium hydride under nitrogen. Anhydrous dichloromethane (CH_2Cl_2) was distilled from P_2O_5 under nitrogen. Anhydrous dimethylformamide (DMF) was distilled from CaH_2 under nitrogen.

Materials: Benzyl bromide, *n*-butyllithium, (3*R*)- and (3*S*)-3,7-dimethyl-6-octenal, decanal, 3,4-dihydro-2*H*-pyran, anhydrous dimethylamine, 2-(4-hydroxy-3-methoxyphenyl)ethanol, 4-hydroxy-3-methoxycinnamaldehyde, nonanal, and vanillin were purchased from Sigma–Aldrich. Pyridinium *p*-toluenesulfonate was prepared as described in the literature.[19]

General Procedure for Short-Column Vacuum Chromatography: The chromatography was carried out using normal-phase Merck silica gel 60 H, which was packed under vacuum in a sintered funnel to form a tightly packed silica bed.[20] To this bed a solution of the compound in dichloromethane was loaded and eluted with stepwise gradient of increased polarity of the mobile phase consisting of hexane and ethyl acetate. Fractions were successively collected and analysed by thin-layer chromatography (TLC). Fractions that had a similar chromatographic profile were combined and the solvent evaporated. Samples were subsequently characterised using NMR and mass spectrometry.

3-Methoxy-4-(tetrahydropyran-2-yloxy)benzaldehyde (1). General Procedure: To a solution of vanillin (5.0 g, 0.033 mol) and pyridinium *p*-toluenesulfonate (0.1 g, 0.004 mol) in anhydrous dichloromethane (50 mL) was added dropwise 3,4-dihydro-2*H*-pyran (3 g, 0.036 mol). The mixture was stirred at room temperature for 24 h.[19] The solvent was removed under reduced pressure to give a residue which was purified by normal-phase short-column vacuum chromatography as described above to afford a colourless liquid, 5.9 g, 76% yield. ^1H NMR ($CDCl_3$): δ = 1.78–1.56 (m, 3 H), 2.15–1.85 (m, 3 H), 3.68–3.59 (m, 1 H), 3.88 (s, 3 H), 3.94–3.89 (m, 1 H), 5.57 (m, 1 H), 7.27 (d, *J* = 8.7 Hz, 1 H), 7.44–7.41 (m, 2 H), 9.86 (s, 1 H) ppm.

3-[3-Methoxy-4-[(tetrahydropyran-2-yl)oxy]phenyl]-2-propenal (2): The synthesis was accomplished according to the general procedure as described for **1** starting with 4-hydroxy-3-methoxycinnamaldehyde (2 g, 0.011 mol). The product was purified by normal-phase short-column vacuum chromatography as described above to afford a yellowish solid, 2.0 g, 70% yield, m.p. 91–92 °C. ^1H NMR ($CDCl_3$): δ = 1.78–1.58 (m, 3 H), 2.10–1.86 (m, 3 H), 3.68–3.61 (m, 1 H), 3.89 (s, 3 H), 3.99–3.90 (m, 1 H), 5.50 (m, 1 H), 6.66–6.58 (dd, *J* = 15.8, 7.7 Hz, 1 H), 7.19–7.09 (m, 3 H), 7.44 (d, *J* = 15.8 Hz, 1 H), 9.67 (d, *J* = 7.7 Hz, 1 H) ppm.

α-(Dimethylamino)nonyl Cyanide (3). General Procedure: To a stirred solution of $NaHSO_3$ (1.0 g, 0.01 mol) in water (2 mL) was added nonanal (2 g, 0.014 mol) in MeOH (30 mL), followed by the addition of anhydrous dimethylamine (0.7 g, 0.016 mol) in cold MeOH (20 mL). The mixture was cooled on ice prior to the addition of an aqueous solution of NaCN (0.8 g, 0.016 mol). The mixture was stirred at room temperature overnight[21,22] and then extracted with Et_2O (2 × 50 mL). The organic portions were washed

with water (20 mL) and evaporated under reduced pressure to give a colourless oil, 2.6 g, 95% yield. The product was used for the next reaction without further purification. ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.39–1.20 (m, 10 H), 1.52–1.40 (m, 2 H), 1.80–1.62 (m, 2 H), 2.31 (s, 6 H), 3.50–3.45 (m, 1 H) ppm.

α-(Dimethylamino)decyl Cyanide (4): The synthesis was accomplished according to the general procedure as described for **3** starting with decanal (2 g, 0.013 mol). A colourless oil, 2.6 g, 94% yield. ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.39–1.20 (m, 12 H), 1.52–1.40 (m, 2 H), 1.80–1.62 (m, 2 H), 2.31 (s, 6 H), 3.50–3.45 (m, 1 H) ppm.

(*R*)-α-(Dimethylamino)-3,7-dimethyl-6-octenyl Cyanide (5): The synthesis was accomplished according to the general procedure as described for **3** starting with (+)-(*R*)-3,7-dimethyl-6-octenal (citronellal) (2 g, 0.013 mol). A colourless oil, 2.5 g, 92% yield. ^{1}H NMR ($CDCl_3$): δ = 0.95–0.92 (m, 3 H), 1.58–1.18 (m, 4 H), 1.60 (s, 3 H), 1.84–1.62 (m, 4 H), 1.99 (m, 2 H), 2.30 (s, 3 H), 2.32 (s, 3 H), 3.60–3.54 (m, 1 H), 5.08 (m, 1 H) ppm.

(*S*)-α-(Dimethylamino)-3,7-dimethyl-6-octenyl Cyanide (6): The synthesis was accomplished according to the general procedure as described for **3** starting with (–)-*S*-3,7-dimethyl-6-octenal (citronellal) (2 g, 0.013 mol). A colourless oil, 2.6 g, 94% yield. ^{1}H NMR ($CDCl_3$): δ = 0.95–0.92 (m, 3 H), 1.58–1.18 (m, 4 H), 1.60 (s, 3 H), 1.84–1.62 (m, 4 H), 1.99 (m, 2 H), 2.30 (s, 3 H), 2.32 (s, 3 H), 3.60–3.54 (m, 1 H), 5.08 (m, 1 H) ppm.

α-(Dimethylamino)-1-{3-methoxy-4-[(tetrahydropyran-2-yl)-oxy]phenyl}acetonitrile (7): The synthesis was accomplished according to the general procedure as described for **3** starting with **1** (2 g, 0.009 mol). A colourless oil, 2.3 g, 95% yield. ^{1}H NMR ($CDCl_3$): δ = 2.10–1.60 (m, 6 H), 2.35 (s, 6 H), 3.60–3.50 (m, 1 H), 3.89 (s, 3 H), 3.96 (m, 1 H), 4.85 (s, 1 H), 5.50 (m, 1 H), 7.10 (m, 2 H), 7.13 (d, J = 8.7 Hz, 1 H) ppm.

(2*E*)-α-(Dimethylamino)-3-{3-methoxy-4-[(tetrahydropyran-2-yl)-oxy]phenyl}-2-propenyl Cyanide (8): The synthesis was accomplished according to the general procedure as described for **3** starting **2** (1 g, 0.004 mol). A colourless oil, 1.1 g, 90% yield. ^{1}H NMR ($CDCl_3$): δ = 1.75–1.58 (m, 3 H), 2.10–1.85 (m, 3 H), 2.37 (s, 6 H), 3.64–3.56 (m, 1 H), 3.88 (s, 3 H), 4.01–3.92 (m, 1 H), 4.44 (dd, J = 4.7, 1.9 Hz, 1 H), 5.44 (m, 1 H), 6.02–5.95 (dd, J = 16, 4.7 Hz, 1 H), 6.88 (dd, J = 16, 1.7 Hz, 1 H), 6.98–6.40 (m, 2 H), 7.12 (d, J = 8.7 Hz, 1 H) ppm.

1-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)undecan-2-one (14). General Procedure: To a solution of diisopropylamine (1.5 mL, 0.01 mol) in dry THF (20 mL) at –80 °C under N_2 was added dropwise *n*-butyllithium (2.5 M, 4 mL, 0.01 mol). The mixture was stirred for 30 min at 0 °C, cooled to –80 °C prior to the addition of a solution of **4** (1.8 g, 0.009 mol) in THF (5 mL). The mixture was stirred at –80 °C for 15 min then brought to room temperature and further stirred for 2 h. To this mixture cooled to –80 °C was added dropwise a solution of **1** (2.0 g, 0.007 mol) in THF (5 mL). The mixture was stirred at –80 °C for 5 h, quenched with wet ether, extracted with Et_2O (2 × 50 mL), washed with brine solution (20 mL) and evaporated to give a residue which was refluxed with aqueous oxalic acid[16,22] (30% w/v) in THF for 1.5 h. The resulting mixture was then extracted with ethyl acetate (2 × 50 mL). After evaporation of solvent, crude product was purified by short-column vacuum chromatography as described above to afford a colourless solid, 1.6 g, 74% yield, m.p. 49–51 °C. ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H), 1.32–1.10 (m, 12 H), 1.58–1.42 (m, 2 H), 2.33 (m, 2 H), 3.87 (s, 3 H), 4.34 (d, J = 4 Hz, 1 H), 5.01 (d, J = 4 Hz, 1 H), 5.71 (s, 1 H), 6.72 (d, J = 2 Hz, 1 H), 6.86 (dd, J = 8, 2 Hz, 1 H), 6.93 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 23.8, 29.0, 29.3 (3C), 29.4, 31.9, 37.8, 56.0, 79.4, 109.1, 114.6, 121.2, 130.0, 146.1, 147.1 ppm. MS (CI): m/z (%) = 337 (10) $[M+29]^+$, 309 (100) $[M+1]^+$, 291 (15), 151 (8). MS (EI): m/z (%) = 308 (8) [M], 151 (100), 55 (8). $C_{18}H_{28}O_4$ (308.20): calcd. C 70.10, H 9.15, O 20.75; found C 70.11, H 9.20, O 20.69.

3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodec-1-en-4-one (15): The synthesis was accomplished according to the general procedure as described for **14** by aldol condensation between **2** (1 g, 0.004 mol) and **3** (0.8 g, 0.004 mol). The product was purified by short-column vacuum chromatography as described above to afford a yellowish oil, 0.8 g, 62% yield. ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, J = 6.8 Hz, 3 H), 1.25 (m, 10 H), 1.63 (m, 2 H), 2.66–2.46 (m, 2 H), 3.91 (s, 3 H), 4.74–4.69 (m, 1 H), 5.70 (s, 2 H), 5.95–5.87 (dd, J = 15, 7.7 Hz, 1 H), 6.76 (d, J = 15 Hz, 1 H), 6.85–7.0 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 23.7, 29.1, 29.2, 29.3, 31.8, 38.1, 55.9, 78.5, 108.5, 114.5, 120.7, 122.9, 128.6, 134.6, 146.1, 146.7 ppm. MS (CI): m/z (%) = 349 (15) $[M+29]^+$, 321 (60) $[M+1]^+$, 303 (100), 197 (50), 137 (40).

3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodecan-4-one (16): To a mixture of **15** (0.6 g, 0.002 mol) and 10% Pd-C as catalyst in ethyl acetate (50 mL) was bubbled through a fine stream of H_2 at room temperature[15] for 4 h. The mixture was filtered, and solvent was removed under reduced pressure to give a colourless residue which was purified by short-column vacuum chromatography to afford the title compound as colourless oil, 0.6 g, 96% yield. ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H), 1.26 (s, 10 H), 1.58 (m, 2 H), 1.84–1.70 (m, 1 H), 2.15–2.04 (m, 1 H), 2.50–2.30 (m, 2 H), 2.80–2.60 (m, 2 H), 3.60 (d, J = 5 Hz, 1 H), 3.88 (s, 3 H), 4.14 (m, 1 H), 5.51 (s, 1 H), 6.71 (m, 2 H), 6.86 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 23.6, 29.1, 29.2, 29.3, 31.0, 31.8, 36.0, 37.9, 55.9, 75.6, 111.3, 114.4, 121.1, 133.1, 143.9, 146.5 ppm. MS (EI): m/z (%) = [M] 322 (20), 150 (95), 137 (100). $C_{19}H_{30}O_4$ (322.21): calcd. C 70.78, H 9.38, O 19.84; found C 70.85, H 9.42, O, 19.73.

4-Benzyloxy-3-methoxybenzaldehyde (9). General Procedure: To a stirred suspension of NaH (60%, 0.6 g, 0.015 mol) in anhydrous DMF (40 mL) at 0 °C under N_2 was added slowly a solution of vanillin (2 g, 0.013 mol) in anhydrous DMF (20 mL) followed by benzyl bromide (2.4 g, 0.014 mol).[23] The mixture was stirred at room temperature for a further 2 h, carefully quenched with cold water, followed by diluted HCl (1 M, 50 mL), then extracted with diethyl ether (2 × 100 mL). The organic layers were combined, washed with water (50 mL) then evaporated under reduced pressure to give a residue which was purified by short-column vacuum chromatography to give a colourless solid, 2.9 g, 92% yield, m.p. 62–64 °C (ref.[24] m.p. 67 °C). ^{1}H NMR ($CDCl_3$): δ = 3.98 (s, 3 H), 5.28 (s, 2 H), 7.03 (d, J = 8 Hz, 1 H), 7.50–7.40 (m, 7 H), 9.87 (s, 1 H) ppm.

(*E*)- and (*Z*)-1-Benzyloxy-2-methoxy-4-(2-methoxyethenyl)benzene (10): To a suspension of (methoxymethyl)triphenylphosphonium bromide (4.0 g, 0.01 mol) in dry THF (50 mL) under N_2 at 0 °C was added dropwise a solution of potassium *tert*-butoxide (1 M, 10 mL, 0.01 mol).[25] The reaction mixture was stirred for further 30 min followed by addition of a solution of **9** (2 g, 0.008 mol) in THF (6 mL). The mixture was stirred at room temperature for 6 h, quenched with cold water, acidified with diluted HCl (1 M, 50 mL), then extracted twice with ethyl acetate (2 × 50 mL). The organic layers were combined, washed with water (50 mL) and evaporated under reduced pressure to give a solid residue, which was purified by short-column vacuum chromatography to give a mixture of (*E*) and (*Z*) isomers as colourless oil, 1.7 g, 78% yield. ^{1}H NMR

($CDCl_3$): δ = 3.66 (s, 3 H), 3.76 (s, 3 H), 3.88 (s, 6 H), 5.13–4.16 (m, 4 H), 5.73 (d, J = 15 Hz, 1 H), 6.04 (d, J = 9 Hz, 1 H), 6.68–6.71 (dd, J = 6, 2 Hz, 1 H), 6.77–6.81 (m, 3 H), 6.91 (d, J = 15 Hz, 1 H), 6.98–7.02 (dd, J = 8, 2 Hz, 1 H), 7.24–7.44 (m, 10 H) ppm.

2-(4-Benzyloxy-3-methoxyphenyl)acetaldehyde (11): To the mixture of **10** (1.0 g, 0.004 mol) in THF (40 mL) was added diluted HCl (1 M, 10 mL). The reaction mixture was reflux for 3 h under N_2, cold water added, then extracted twice with diethyl ether (2 × 100 mL). The combined organic layer was washed with water (50 mL) and removed under reduced pressure to afford a residue, which was purified by column chromatography to give a colourless oil,[11] 0.6 g, 60% yield. ^{1}H NMR ($CDCl_3$): δ = 3.61 (d, J = 2 Hz, 2 H), 3.89 (s, 3 H), 5.15 (s, 2 H), 6.71 (dd, J = 8, 2 Hz, 1 H), 6.73 (d, J = 2 Hz, 1 H), 6.88 (d, J = 8 Hz, 1 H), 7.50–7.26 (m, 5 H), 9.72 (t, J = 2 Hz, 1 H) ppm.

1-(4-Benzyloxy-3-methoxyphenyl)-2-hydroxydodecan-3-one (12): The synthesis was accomplished according to the general procedure as described for **14** by an aldol condensation between **4** (0.25 g, 0.001 mol) and **11** (0.3 g, 0.001 mol). The product was purified by short-column vacuum chromatography to give a colourless solid, 0.35 g, 85% yield. ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.26 (m, 12 H), 1.60 (m, 2 H), 2.55–2.37 (m, 2 H), 2.83–2.76 (dd, J = 14, 7.4 Hz, 1 H), 3.09–3.03 (dd, J = 14, 4.6, Hz, 1 H), 3.41 (d, J = 5 Hz, 1 H), 3.88 (s, 3 H), 4.41–4.30 (m, 1 H), 5.13 (s, 2 H), 6.70 (dd, J = 8, 2 Hz, 1 H), 6.82–6.79 (m, 2 H), 7.45–7.26 (m, 5 H) ppm. MS (CI, NH_4): m/z (%) = 430 (100) $[M+18]^+$, 414 (35), 358 (25). MS (EI): m/z (%) = 412 (8) [M], 227 (40), 137 (35), 91 (100).

2-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodecan-3-one (17): The synthesis was accomplished according to the general procedure as described for **16** starting **12** (0.35 g, 0.9 mmol). The product was purified by short-column vacuum chromatography to give a colourless solid, 0.27 g, 92% yield, m.p. 46–48 °C. ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.26 (m, 12 H), 1.58 (m, 2 H), 2.56–2.38 (m, 2 H), 2.84–2.77 (dd, J = 14, 7.4 Hz, 1 H), 3.09–3.03 (dd, J = 14, 4.6 Hz, 1 H), 3.42 (d, J = 5 Hz, 1 H), 3.88 (s, 3 H), 4.42–4.35 (m, 1 H), 5.53 (s, 1 H), 6.71 (dd, J = 8, 2 Hz, 1 H), 6.77 (d, J = 2 Hz, 1 H), 6.85 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 23.6, 29.2, 29.3, 29.4, 29.4, 31.9, 38.7, 39.9, 55.9, 77.4, 111.8, 114.4, 121.9, 128.4, 144.6, 146.5 ppm. MS (CI): m/z (%) = 323 (15) $[M+1]^+$, 305 (70), 291 (12), 137 (100). MS (EI): m/z (%) = [M] 322 (5), 137 (100). $C_{19}H_{30}O_4$ (322.21): calcd. C 70.78, H 9.38, O 19.84; found C 71.04, H 9.46, O 19.50.

(2*RS*,5*R*)-2-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-5,9-dimethyldec-8-en-3-one (18): The synthesis was accomplished according to the general procedure as described for **14** via aldol condensation between **5** (0.2 g, 0.001 mol) and **11** (0.3 g, 0.001 mol). The product was purified by short-column vacuum chromatography to give a colourless oil (**13**), 0.32 g, 78% yield. To this oil (0.32 g) was added ethanol (10 mL), cyclohexene (5 mL) and Pd-C (10%, 0.02 g).[16] The mixture was stirred under reflux for 3 h, filtered and the solvent evaporated under reduced pressure to give an oil which was purified by short-column vacuum chromatography to afford a colourless oil, 0.2 g, 80% yield. ^{1}H NMR ($CDCl_3$): δ = 0.91–0.88 (m, 3 H), 1.38–1.18 (m, 2 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 2.15–1.88 (m, 3 H), 2.36–2.26 (m, 1 H), 2.52–2.42 (m, 1 H), 2.81–2.72 (m, 1 H), 3.10–3.03 (m, 1 H), 3.45–3.42 (m, 1 H), 3.88 (s, 3 H), 4.39–4.30 (m, 1 H), 5.12–5.04 (m, 1 H), 5.53 (s, 1 H), 6.72 (dd, J = 8, 2 Hz, 1 H), 6.78 (d, J = 2 Hz, 1 H), 6.85 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9, 25.5, 25.7, 28.9, 37.0, 39.8, 45.9, 55.9, 77.4, 77.9, 111.9, 114.3, 121.9, 124.1, 128.4, 131.8, 144.6, 146.5 ppm. MS (CI): m/z (%) = 321 (30) $[M+1]^+$, 303 (100), 165 (15), 137 (80). MS (EI): m/z (%) = 320 (20) [M], 137 (100). $C_{19}H_{28}O_4$ (320.20): calcd. C 71.22, H 8.81, O 19.97; found C 70.87, H 8.82, O 20.31.

(2*RS*,5*S*)-2-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-5,9-dimethyldec-8-en-3-one (19): Synthesis of the title compound was accomplished similar to that described for **18**. The product was purified by short-column vacuum chromatography to afford a colourless oil, 0.2 g, 82% yield. ^{1}H NMR ($CDCl_3$): δ = 0.91–0.88 (m, 3 H), 1.38–1.18 (m, 2 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 2.10–1.90 (m, 3 H), 2.36–2.28 (m, 1 H), 2.51–2.42 (m, 1 H), 2.81–2.72 (m, 1 H), 3.10–3.03 (m, 1 H), 3.45–3.42 (m, 1 H), 3.88 (s, 3 H), 4.39–4.30 (m, 1 H), 5.10–5.02 (m, 1 H), 5.53 (s, 1 H), 6.70 (dd, J = 8, 2 Hz, 1 H), 6.78 (d, J = 2 Hz, 1 H), 6.83 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9, 25.5, 25.7, 28.9, 36.9, 39.8, 46.0, 55.9, 77.4, 77.9, 111.9, 114.3, 121.9, 124.1, 128.4, 131.8, 144.6, 146.5 ppm. MS (CI): m/z (%) = 321 (25) $[M+1]^+$, 303 (80), 225 (25), 166 (20), 137 (100). MS (EI): m/z (%) = 320 (5) [M], 137 (100). $C_{19}H_{28}O_4$ (320.20): calcd. C 71.22, H 8.81, O 19.97; found C 71.40, H 8.85, O 19.75.

2-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)undecan-1-one (20): The synthesis was accomplished according to the general procedure as described for **14** via aldol condensation between **7** (1 g, 0.003 mol) and decyl aldehyde (0.5 g, 0.003 mol). The product was purified by short-column vacuum chromatography to give a colourless solid, 0.8 g, 85% yield, m.p. 78–79 °C. ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H), 1.24 (m, 12 H), 1.62–1.48 (m, 3 H), 1.84 (m, 1 H), 3.7 (m, 1 H), 3.97 (s, 3 H), 5.02 (m, 1 H), 6.20 (s, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 7.48 (dd, J = 8.2, 2 Hz, 1 H), 7.53 (d, J = 2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2, 22.7, 24.9, 29.3, 29.4, 29.5, 29.5, 31.9, 36.61, 56.2, 72.7, 110.4, 114.1, 123.9, 126.4, 146.9, 151.1 ppm. MS (CI): m/z (%) = 337 (5) $[M+29]^+$, 309 (25) $[M+1]^+$, 291 (100), 153 (8). MS (EI): m/z (%) = 308 (4) [M], 153 (100), 125 (10), 93 (20), 65 (15), 55 (14). $C_{18}H_{28}O_4$ (308.20): calcd. C 70.10, H 9.15, O 20.75; found C 70.20, H 9.18, O 20.62.

4-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodec-1-en-3-one (21): The synthesis was accomplished according to the general procedure as described for **14** via aldol condensation between **8** (0.6 g, 0.002 mol) and nonyl aldehyde (0.3 g, 0.002 mol). The product was purified by short-column vacuum chromatography to give a yellowish oil, 0.4 g, 65% yield. ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H), 1.25 (m, 10 H), 1.62–1.38 (m, 3 H), 1.94–1.82 (m, 1 H), 3.68 (d, J = 5 Hz, 1 H), 3.96 (s, 3 H), 4.50–4.43 (m, 1 H), 6.05 (s, 1 H), 6.71 (d, J = 15.9 Hz, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 7.07 (d, J = 2 Hz, 1 H), 7.18 (dd, J = 8.2, 2 Hz, 1 H), 7.72 (d, J = 15.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 25.0, 29.3, 29.5, 29.6, 31.9, 34.6, 56.1, 75.6, 109.9, 114.9, 118.2, 123.8, 126.7, 144.9, 146.9, 148.8 ppm. MS (CI): m/z (%) = 361 (5) $[M+41]^+$, 349 (15) $[M+29]^+$, 321 (100) $[M+1]^+$, 303 (10). MS (EI): m/z (%) = 320 (10) [M], 177 (100), 145 (20), 77 (12), 43 (12).

4-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodecan-3-one (22): Hydrogenation of **21** (0.2 g) was carried out under H_2 in the presence of 10% Pd-C as described for **16**. The product was purified by short-column vacuum chromatography to give a colourless solid, 0.2 g, 95% yield, m.p. 40–41 °C. ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 6.8 Hz, 3 H), 1.25 (m, 11 H), 1.54–1.36 (m, 2 H), 1.83–1.72 (m, 1 H), 2.80–2.65 (m, 2 H), 2.96–2.82 (m, 2 H), 3.43 (d, J = 5 Hz, 1 H), 3.87 (s, 3 H), 4.15–4.10 (m, 1 H), 5.50 (s, 1 H), 6.68–6.64 (m, 2 H), 6.84 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 24.8, 29.2, 29.4, 29.4, 29.5, 31.9, 33.7, 40.0, 55.9, 76.7, 111.0, 114.5, 120.8, 132.5, 143.9, 146.4 ppm. MS (EI): m/z (%) = 322 (40) [M], 180 (40), 152 (45), 137 (100), 124 (40). $C_{19}H_{30}O_4$ (322.21): calcd. C 70.78, H 9.38, O 19.84; found C 70.79, H 9.38, O 19.83.

Molecular Modeling: Molecular construction was carried out using Maestro version 6.0.107, MM share version 1.2.014, Shrodinger,

L.L.C. Molecular models were energy-minimized with default settings for molecular modeling force field, then superimposed to compound **17** with the following atom pairs: each of the oxygen atoms attached to the aromatic ring, oxygen attached to the 3rd atom of the major chain, 3rd and 7th atom of the major chain. The best fit was selected from low-energy conformers.

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