Synthesis and Olfactory Properties of Seco-Analogues 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 a set of racemic seco-analogues of such natural products. The synthesis employs commercially available α-chloroketones as substrates that are transformed in four steps to target compounds. Their qualitative olfactory analysis revealed that the opening of the tetrahydrofuran ring leads to a vanishing of original flowery scent with the emergence of spicy aroma accompanied by green notes, and/or fruity aspects of novel seco-analogues. These results suggest the important osmophoric role of THF moiety for the generation of the typical flowery aroma associated with lilac aldehydes.

Keywords: terpenes; structural design; natural products; olfactory evaluation

1. Introduction

Lilac aldehydes 1 (Figure 1) were first isolated in 1974 from an oil [1] of lilac flowers (Syringa vulgaris L., Oleaceae). Being considered as important phytovolatiles, structure elucidation and olfactometric analysis of all stereoisomers was performed [2]. Consequently, the biosynthesis of lilac aldehydes was proposed and investigated [3]. Since then, these naturally occurring monoterpenes were found in flowers of many other species, including kiwifruit [4], the White Campion [5], and the Lesser Butterfly orchid [6]. Thus, fragrant lilac aldehydes represent an attractive olfactory target for insect pollinators. It is known that these flower-scenting molecules are much sought after by (nocturnal) moth species [7–9], butterflies [10,11], and even mosquitos [12–14]. In this context, lilac aldehydes are being developed as chemical markers of the botanical origin of honeys [15–18]. Interestingly, lilac aldehydes were recently found as odour-active compounds in oysters, and thus, could be potentially used as freshness indicators for this delicacy [19]. For perfumery purposes, synthetically prepared lilac aldehydes are used almost exclusively. Interestingly, the major naturally occurring (5′S)-stereoisomers 1a–d have a lower odour threshold by 1–2 orders of magnitude in comparison to lilac aldehydes 1e–h with (5′R)- absolute configuration [2] (Figure 1).

Up to date, numerous syntheses of racemic [4,8,20–25] and enantiomerically pure lilac aldehydes 1 are known [2,26–28]. Recently, we have published the first comprehensive study investigating the importance of respective substituents on the genuine flowery odour of lilac aldehydes. We have found [29] that the addition of methyl group to C-2 stereogenic centre of lilac aldehydes 1 significantly shifts the original flowery odour to a rather herbal scent of their unnatural homologues 2. In addition, various functional groups have only minimal effect on the scent variations (Figure 2).

As a continuation of our research, we decided to investigate the influence of tetrahydrofuran ring and/or alkene moiety on the olfactory properties of C-2 methylated homologues of lilac aldehydes 2. Thus, we have devised a new set of (racemic) seco-analogues 3–7 featuring a higher conformational freedom and/or variable substitution pattern of the C=C bond (Figure 3).
2. Results and Discussion

The preparation of novel seco-analogues 3–7 features a common synthetic strategy that starts with an acid-catalysed ketalisation of commercially available α-chloroketones 8–11 with neopentyl glycol followed by elimination of intermediary chloroketals 12–15 under basic conditions [30]. Unlike the chlorocyclopentane ketal 14, the elimination of chlorocyclohexane ketal 15 provided an inseparable mixture of desired cyclohexene ketal 19 and its regioisomer 25 in a ratio of 5:1 (based on the integration of respective olefinic signals in $^{1}H$ NMR spectrum). Thus, the obtained alkenyl ketals 16–19 were reductively opened either by diisobutyl aluminium hydride [31] or methyl magnesium bromide [32] to furnish the corresponding alcohols 20–24. In case of DIBAL reduction of mixture of ketals 19 + 25, only 19 was opened while 25 remained untouched under the reaction conditions. This enabled the efficient FLC separation of unreacted ketal 25 from desired alcohol 24. Eventually, the final Dess–Martin oxidation [33] of pure alcohols 20–24 provided target aldehydes 3–7 in overall yields of 2–21% over four steps (Scheme 1).
Table 1. Olfactory properties of compounds 3–7, 20–24 prepared via Scheme 1.

| Alcohol | Aroma                                | Aldehyde | Aroma                         |
|---------|--------------------------------------|----------|-------------------------------|
| ![](image.png) 20 | Sweet, herbal, minty, eucalyptic      | ![](image.png) 3 | Spicy, terpenic, pungent     |
| ![](image.png) 21 | Balsamic, pleasant, minty, eucalyptic | ![](image.png) 4 | Spicy, camphor, sharp, with green notes |

With seco-analogues of lilac aldehydes 3–7 in our hands, we have undertaken their qualitative sensory evaluation. Since lilac alcohols also contribute to the complex scent of lilac flowers, we have also included their acyclic analogues 20–24 in the olfactory screening. The results are summarised in Table 1. Evidently, the opening of the tetrahydrofuran ring leads to a vanishing of flowery scent typical for lilac aldehydes 1, suggesting the important olfactophoric role of THF moiety. Thus, ring-opened analogues 3–5 bearing an acyclic alkene exhibit a rather common spicy, sharp aroma with green/herbal notes. The scent of their congeners featuring a cyclic alkene is further shifted towards sweet, fruity aspects for 6 and herbal, green notes for 7. Interestingly and for comparison, while the respective alcohols 20, 22, 23, and 24 commonly exhibit sweet(ish) aroma with oily/fatty and turpentine-like facets, alcohol 21 features a pleasant balsamic aroma with minty-eucalyptic notes. Finally, the odour intensity for target compounds was rather weak to moderate with only short aroma persistence in a range of tens of minutes.
Table 1. Cont.

| Alcohol | Aroma                                | Aldehyde | Aroma                        |
|---------|--------------------------------------|----------|------------------------------|
| HO–O=C=O | Oily, sweetish, turpentine-like      | O=C=O    | Herbal, green, sweetish, ethereal, sharp |
| HO–O=C=   | Fruity-sweetish, fatty, turpentine   | O=C=O    | Sweet, fruity, with eucalyptus notes |
| HO–O=C=   | Bitter-sweet, turpentine-like        | O=C=O    | Herbal, slightly green, with earthy notes |

3. Materials and Methods

3.1. Materials and Methods

Chemicals and reagents were purchased from commercial sources (Alfa Aesar, Sigma-Aldrich) and were used without further purification. Anhydrous solvents were prepared by distillation and standing over activated 4Å molecular sieves under argon atmosphere. Hexanes refer to a mixture of C-6 alkanes (b.p. 60–80 °C). Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on aluminium sheets pre-coated with silica gel 60 F_{254} (Merck). Visualisation was performed using short-wave UV light followed by dipping TLC plates in either basic solution of KMnO₄, acidic solution of vanillin or acidic solution of ceric ammonium nitrate followed by heating with a heat gun. Preparative thin layer chromatography (PTLC) was carried out on glass plates (20 × 20 cm) coated with PLC silica gel 60 (layer thickness 1 mm) with concentrating zone (20 × 4 cm). Flash column chromatography (FLC) was performed using Silica Gel 60 (particle size 40–63 µm). Medium-pressure liquid chromatography (MPLC) was performed using a Büchi Sepacor System equipped with Pump Module C-615 and Fraction Collector C-660 using silica gel (particle size 15–40 µm). NMR spectra were recorded in CDCl₃ on a Varian INOVA 300 (300 MHz for 1H, 75 MHz for 13C nuclei), Varian 400-MR (399.9 MHz for 1H, 100.6 MHz for 13C nuclei) or Varian VNMR 600 (600 MHz for 1H, 151 MHz for 13C nuclei) NMR spectrometer and were correctly shifted using residual non-deuterated solvent as an internal reference (CHCl₃: δC = 77.16 ppm (central peak of a 1:1:1 triplet). Chemical shifts (δ) are quoted in ppm. Liquid chromatography-mass spectrometry (LC-MS) analyses were performed on Agilent 1200 Series instrument equipped with a multimode MS detector using the MM ESI/APCI ionisation method (column Zorbax Eclipse XDB-C18, 150 × 4.6 mm, particle size 5 µm, eluent water with 0.1% HCO₂H/CH₃CN, 70:30, flow 1.5 mL/min). High-resolution mass spectra (HR-MS) were recorded on a Thermo Scientific Orbitrap Velos mass spectrometer with a heated electrospray ionisation (HESI) source in positive and/or negative mode. FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron) equipped with a Smart Orbit (diamond crystal ATR) accessory using the reflectance technique (4000–400 cm⁻¹). The sensory analysis was performed by authors in a clean and odourless environment at 22 °C by using testing strips of odourless absorbent paper. This was wetted with the tested compound and the paper strip was smelled at certain intervals, while the scent was recorded.

3.2. Synthetic Procedures and Analytical Data

3.2.1. General Experiment for the Preparation of Chloroketals (12–15)

A stirred solution of chloroketone 8–11, 2,2-dimethyl-1,3-propanediol (1.0 or 1.2 equiv) and p-TsOH·H₂O (0.023 equiv) in cyclohexane (c = 0.7 M) was refluxed in a round bottom flask equipped with a Dean–Stark apparatus. After the indicated time, the mixture was...
cooled to RT and solvent was evaporated in vacuo (bath temperature 50–55 °C, pressure 30–50 mbar) and the resulting oil dissolved in Et2O. The ethereal solution was sequentially washed with sat. aq. NaHCO3 soln., water and brine, dried (MgSO4) and concentrated in vacuo (35 °C, 30 mbar). The obtained crude product was further used as such or purified either by bulb-to-bulb vacuum distillation (Kugelrohr) or FLC to furnish a corresponding chloroketal 12–15. The structural characterization (1H-NMR, 13C-NMR spectra) of the new compound are presented in Supplementary Materials.

2-(1-Chloroethyl)-2,5,5-trimethyl-[1,3]dioxane (12)
Prepared accordingly to Ref. [30]: commercial 3-chlorobutanone 8 (5.86 mL, 56 mmol), 2,2-dimethyl-1,3-propanediol (2.36 g, 23 mmol), p-TsOH·H2O (246 mg, 1.3 mmol), cyclohexane (81 mL), reflux (100 °C), 17 h, concentrated in vacuo (55 °C, 50 mbar), Et2O (61 mL), NaHCO3 (37 mL), water (37 mL), brine (37 mL), crude chloroketal 12 (9.79 g, 90%) as yellow oil; Rf (hexanes/AcOEt 5:1) 0.74; δH (300 MHz, CDCl3) 4.14 (q, J = 6.8 Hz, 1H, CHCl), 3.61 (dd, J = 11.5, 8.9 Hz, 2H, OCH2), 3.52–3.40 (m, 2H, OCH2), 1.53 (d, J = 6.8 Hz, 3H, Me), 1.46 (s, 3H, Me), 1.08 (s, 3H, Me2), 0.85 (s, 3H, Me2). NMR spectrum fully corresponds to the literature data [30]; m/z (ESI) 157.2 (100, M+Cl−), 158.0 (9%), 175.2 (76, M+Cl+H2O+), 176.0 (8%), tR = 2.34 min.

2-(1-Chloroethyl)-2-ethyl-5,5-dimethyl-[1,3]dioxane (13)
2-Chloropentan-3-one 9 (2.73 g, 23 mmol, prepared accordingly to Ref. [34]), 2,2-dimethyl-1,3-propanediol (2.36 g, 23 mmol), p-TsOH·H2O (99 mg, 0.52 mmol), cyclohexane (32.6 mL), reflux (130 °C), 27 h, concentrated in vacuo (50 °C, 45 mbar), Et2O (40 mL), NaHCO3 (30 mL), water (30 mL), brine (30 mL), FLC (176 g SiO2, Hex: Et2O 12:1, 650 mL), pure chloroketal 13 (2.41 g, 51%) as colourless oil; Rf (hexanes/AcOEt 6:1) 0.67; νmax (ATR) 2956, 2869, 1469, 1396, 1186, 1142, 1126, 1093, 1081, 1016, 957, 916 cm−1; δH (600 MHz, CDCl3) 4.35 (q, J = 6.8 Hz, 1H, CHCl), 3.59 (d, J = 11.5 Hz, 1H, OCH2), 3.55 (d, J = 11.5 Hz, 1H, OCH2), 3.49 (d, J = 11.5 Hz, 1H, OCH2), 3.48 (d, J = 11.5 Hz, 1H, OCH2), 1.96 (m, 2H, CH2), 1.55 (d, J = 6.8 Hz, 3H, Me), 1.04 (s, 3H, Me2), 0.93 (t, J = 7.5 Hz, 3H, Me), 0.90 (s, 3H, Me2); δC (151 MHz, CDCl3) 100.1 (OCO), 70.2 (2 × OCH2), 56.5 (CHCl), 29.6 (Cq), 22.9 (Me2), 22.5 (Me2), 21.2 (CH2), 18.7 (Me), 7.0 (Me); m/z (ESI) 189.2 (100, M+Cl+H2O+), 190.0 (10%), 171.2 (95, M+Cl−), 172.2 (8%), tR = 2.96 min; HR-MS (HESI): M+, found 170.1305. C10H13O2 requires 170.1301.

1-Chloro-8,8-dimethyl-6,10-dioxaspiro[4.5]decane (14)
Commercial 2-chlorocyclopentanone 10 (755 µL, 7.5 mmol), 2,2-dimethyl-1,3-propanediol (943 mg, 9.1 mmol), p-TsOH·H2O (33 mg, 0.17 mmol), cyclohexane (11 mL), reflux (128 °C), 4.5 h, concentrated in vacuo (50 °C, 50 mbar). Et2O (15 mL), NaHCO3 (6 mL), water (6 mL), brine (6 mL), FLC (41 g SiO2, Hex: AcOEt 6:1, 270 mL), pure chloroketal 14 (1.27 g, 82%) as colourless oil; Rf (hexanes/AcOEt 5:1) 0.67; νmax (ATR) 2954, 2867, 1472, 1396, 1337, 1207, 1144, 1112, 1076, 1016, 837 cm−1; δH (300 MHz, CDCl3) 4.39–4.34 (m, 1H, CHCl), 3.55–3.45 (m, 4H, 2 × OCH2), 2.29–1.60 (m, 6H, 3xCH2), 1.00 (s, 3H, Me2), 0.98 (s, 3H, Me2); δC (151 MHz, CDCl3) 107.6 (OCq), 72.3 (OCH2), 72.1 (OCH2), 60.7 (CHCl), 32.9 (CH2), 31.1 (CH2), 30.0 (Cq), 22.4 (Me2), 22.3 (Me2), 18.6 (CH2); HR-MS (HESI): M+, found 204.0913. C10H15ClO2 requires 204.0912.

7-Chloro-3,3-dimethyl-1,5-dioxaspiro[5.5]undecane (15)
Commercial 2-chlorocyclohexane 11 (860 µL, 7.5 mmol), 2,2-dimethyl-1,3-propanediol (942 mg, 9.0 mmol), p-TsOH·H2O (33 mg, 0.17 mmol), cyclohexane (10.9 mL), reflux (160 °C), 10 h, concentrated in vacuo (55 °C, 50 mbar). Et2O (20 mL), NaHCO3 (5 mL), water (5 mL), brine (5 mL), bulb-to-bulb distillation (175–180 °C, 27 mbar), pure chloroketal 15 (1.43 g, 87%) as yellow oil; Rf (hexanes/AcOEt 5:1) 0.67; νmax (ATR) 2942, 2864, 1472, 1446, 1395, 1364, 1215, 1167, 1112, 1111, 1096, 1016, 965, 804 cm−1; δH (600 MHz, CDCl3) 4.23–4.18 (m, 1H, CHCl), 3.62 (d, J = 11.4 Hz, 1H, OCH3), 3.58 (d, J = 11.5 Hz, 1H, OCH2), 3.52 (dd, J = 11.4, 1.8 Hz,
1H, OCH2), 3.45 (dd, J = 11.4, 1.8 Hz, 1H, OCH2), 2.33–2.23, 2.07–2.00, 1.96–1.88, 1.76–1.68 (4×m, 4 × 1H, 2 × CH2), 1.57–1.37 (m, 4H, 2 × CH2), 1.12 (s, 3H, Me2), 0.87 (s, 3H, Me2). 1H NMR spectrum fully corresponds the literature data [35]; δC (151 MHz, CDCl3) 97.2 (OCH2), 70.3 (OCH2), 69.8 (OCH2), 61.6 (CHCl), 32.0 (Cq, CH2), 30.0 (CH2), 27.4 (CH2), 22.8 (Me2), 22.4 (Me2), 21.6 (CH2); HR-MS (HESI): M+, found 218.1071. C11H10ClO2 requires 218.1068.

3.2.2. General Experiment for the Preparation of Alkene Ketals (16–19, 25)

To a stirred solution of potassium hydroxide (11 eq.) in ethylene glycol was added to chloroketal 12–15 at 120 °C and the reaction mixture was heated at 160 °C for 7–23 h. After cooling to RT, water was added and extracted with Et2O. The organic phase was washed with water and brine, dried (MgSO4) and concentrated in vacuo (35 °C, 30–200 mbar). The crude product was purified either by bulb-to-bulb vacuum distillation (Kugelrohr) or FLC to furnish a corresponding ketal 16–19, 25.

2,5,5-Trimethyl-2-vinyl-[1,3]dioxiane (16)

KOH (31.72 g, 0.57 mol), ethylene glycol (68 mL), chloroketal 12 (9.76 g, 51 mmol), 23 h, water (340 mL), Et2O (3 × 150 mL), water (110 mL), brine (110 mL), concentrated in vacuo (35 °C, 30 mbar), bulb-to-bulb vacuum distillation (80–95 °C, 27 mbar), ketal 16 (4.76 g, 60%) as colourless oil; Rf (hexanes/AcOEt 5:1) 0.72; δH (300 MHz, CDCl3) 5.76 (dd, J = 17.8, 10.8 Hz, 1H, C=C), 5.38 (dd, J = 13.6, 1.5 Hz, 1H, CH=CH2), 5.33 (dd, J = 6.6, 1.5 Hz, 1H, CH=CH2), 1.17 (s, 3H, Me), 1.10 (s, 3H, Me), 0.70 (s, 3H, Me2). NMR spectrum is in accordance with the literature data [30].

2-Ethyl-5,5-dimethyl-2-vinyl-[1,3]dioxiane (17)

KOH (7.46 g, 0.13 mol), ethylene glycol (16 mL), chloroketal 13 (2.46 g, 12 mmol), 21 h, water (200 mL), Et2O (3 × 80 mL), water (80 mL), brine (80 mL), concentrated in vacuo (35 °C, 200 mbar), FLC (112 g SiO2, DCM, 400 mL), ketal 17 (1.44 g, 71%) as colourless oil; Rf (DCM) 0.54; νmax (ATR) 2952, 2870, 1471, 1403, 1395, 1363, 1179, 1154, 1085, 955, 914 cm⁻¹; δH (600 MHz, CDCl3) 5.66 (dd, J = 17.7, 11.0 Hz, 1H, CH=CH2), 5.40 (dd, J = 11.0, 1.6 Hz, 1H, CH=CH2), 5.33 (dd, J = 17.8, 1.6 Hz, 1H, CH=CH2), 3.61 (d, J = 11.0 Hz, 2H, OCH2), 3.32 (d, J = 11.2 Hz, 2H, OCH2), 1.65 (q, J = 7.5 Hz, 2H, CH2), 1.17 (s, 3H, Me2), 0.92 (t, J = 7.5 Hz, 3H, Me), 0.69 (s, 3H, Me); δC (151 MHz, CDCl3) 137.4 (CH=CH2), 119.0 (CH=CH2), 100.5 (OCH2), 71.5 (2 × OCH2), 34.5 (CH2), 30.2 (Cq, 22.8 (Me2), 22.0 (Me2), 7.1 (Me); m/z (ESI) 171.2 (82, M+H+), 172.2 (8%), tR = 2.89 min; HR-MS (HESI): M+, found 170.1301. C10H13O2 requires 170.1301.

8,8-Dimethyl-6,10-dioxaspiro[4.5]dec-1-ene (18)

KOH (3.88 g, 69 mmol), ethylene glycol (8.3 mL), chloroketal 14 (1.27 g, 6.2 mmol), 7 h, water (90 mL), Et2O (3 × 50 mL), water (50 mL), brine (50 mL), concentrated in vacuo (35 °C, 30 mbar), bulb-to-bulb vacuum distillation (125–130 °C, 28 mbar), ketal 18 (0.62 g, 60%) as yellow oil; Rf (hexanes/AcOEt 6:1) 0.51; νmax (ATR) 2952, 2855, 1473, 1395, 1363, 1203, 1141, 1129, 1088, 1048, 1036, 955, 908, 894 cm⁻¹; δH (600 MHz, CDCl3) 6.16 (dt, J = 5.8, 2.2 Hz, 1H, CH=CH2) 6.10 (dt, J = 5.9, 2.4 Hz, 1H, CH=CH2), 3.59 (d, J = 11.3 Hz, 2H, OCH2) 3.53 (d, J = 11.3 Hz, 2H, OCH2), 2.42 (dt, J = 7.5, 6.7, 2.3 Hz, 2H, CH2), 2.14–2.11 (m, 2H, CH2), 1.01 (s, 3H, Me2), 0.98 (s, 3H, Me2); δC (151 MHz, CDCl3) 136.9 (CH=CH2), 128.9 (CH=CH2), 111.9 (OCH2) 72.5 (2 × OCH2), 33.4 (CH2), 30.0 (Cq), 29.6 (CH2), 22.6 (Me2), 22.4 (Me2); HR-MS (HESI): M+, found 168.1144. C10H16O2 requires 168.1145.

3,3-Dimethyl-1,5-dioxaspiro[5.5]undec-7-ene (19) and 3,3-Dimethyl-1,5-dioxaspiro[5.5]undec-8-ene (25)

KOH (2.86 g, 51 mmol), ethylene glycol (6.1 mL), chloroketal 15 (1.0 g, 4.6 mmol), 18.5 h, water (60 mL), Et2O (3 × 20 mL), water (20 mL), brine (20 mL), concentrated in vacuo (35 °C, 30 mbar), bulb-to-bulb vacuum distillation (145–155 °C, 27 mbar) to give a mixture
of ketalts 19:25 in ratio 5:1 determined by 1H NMR spectroscopy (0.69 g, 83%) as colourless oil; Rf (hexanes/AcOEt 5:1) 0.59.

Ketal (19): δH (600 MHz, CDCl3) 6.10 (dt, J = 10.4, 2.1 Hz, 1H, CH=CH2), 5.92 (dt, J = 10.3, 3.6 Hz, 1H, CH=CH2), 3.62 (d, J = 11.4 Hz, 2H, OCH2), 3.51 (d, J = 11.4 Hz, 2H, OCH2), 2.07–2.03 (m, 2H, CH2), 1.93–1.90 (m, 2H, CH2), 1.75–1.70 (m, 2H, CH2), 1.02 (s, 3H, Me2), 0.95 (s, 3H, Me2), δc (151 MHz, CDCl3) 132.1 (CH=CH2), 125.2 (CH=CH2), 95.1 (OCq), 70.4 (2 × OCH2), 32.0 (CH2), 30.1 (Cq), 25.6 (CH2), 22.8 (Me2), 22.6 (Me2), 19.3 (CH3); m/z (ESI) 183.0 (53, M+H+), 184.0 (7%), tR = 2.24 min.

Ketal (25): δmax (ATR) 3027, 2952, 2861, 1470, 1361, 1269, 1251, 1105, 1036, 1015, 845 cm−1; δH (600 MHz, CDCl3) 5.70–5.66 (m, 1H, CH=CH2), 5.58–5.54 (m, 1H, CH=CH2), 3.59 (d, J = 11.5 Hz, 2H, OCH2), 3.49 (d, J = 11.5 Hz, 2H, OCH2), 2.39–2.35 (m, 2H, CH2), 2.16–2.11 (m, 2H, CH2), 1.96 (t, J = 6.5 Hz, 2H, CH2), 1.03 (s, 3H, Me2), 0.92 (s, 3H, Me2); δc (151 MHz, CDCl3) 126.4 (CH=CH2), 123.4 (CH=CH2), 97.0 (OCq), 70.2 (2 × OCH2), 34.8 (CH2), 30.2 (Cq), 27.3 (CH2), 23.5 (CH2), 22.8 (Me2), 22.5 (Me2); HR-MS (HESI): M+ requires 183.1316. C11H15O2 requires 182.1301.

3.2.3. Preparation of Alcohol (21)

To a stirred solution of ketal 16 (0.3 g, 1.9 mmol) in anhydrous toluene (32 mL) was added 3M solution of MeMgBr in diethyl ether (6.4 mL, 19.2 mmol, 10 equiv) drop-wise at 0 °C. To a stirred solution of ketal 16 (0.3 g, 1.9 mmol) in anhydrous toluene (32 mL) was added 3M solution of MeMgBr in diethyl ether (6.4 mL, 19.2 mmol, 10 equiv) drop-wise at 0 °C. The reaction was carefully quenched with sat. aq. NH4Cl soln. (25 mL) and water (10 mL). The layers were separated and the aqueous phase was extracted with Et2O (3 × 15 mL). The combined organic layers were washed with brine (30 mL) and dried over Na2SO4. The solvents were evaporated in vacuo (75 °C, 29 mbar) and crude material was purified by MPLC (16 g SiO2, flow 50 mL/min, fraction 5 mL, gradient elution hexanes/AcOEt 90:10 → 50:50) to furnish alcohol 21 (75 mg, 23%) as colourless oil; Rf (hexanes/AcOEt 5:1) 0.37; δmax (ATR) 3433 (OH), 2870, 2976, 2954, 2861, 1470, 1455, 1415, 1360, 1150, 1076, 1044, 999, 920, 874 cm−1; δH (400 MHz, CDCl3) 4.21 (q, J = 7.7 Hz, 3H, CH3), 3.27 (d, J = 7.7 Hz, 2H, OCH2), 2.44 (t, J = 7.7 Hz, 2H, OCH2), 1.93 (t, J = 7.7 Hz, 2H, OCH2), 1.03 (s, 3H, Me2), 0.95 (s, 3H, Me2), 0.93 (s, 3H, Me2); δc (101 MHz, CDCl3) 143.5 (CH=CH2), 114.1 (CH=CH2), 75.2 (OCq), 72.7 (CH2), 72.6 (CH2), 35.5 (Cq), 25.6 (Me2), 22.0 (Me2); HR-MS (HESI): M+ found 172.1466. C10H16O2 requires 172.1463.

3.2.4. General Experiment for the Preparation of Alcohols (20, 22, 23)

To a stirred solution of ketal 16–18, anhydrous THF was added dropwise to a solution of DIBAL in toluene (1.0 M, 5–10 equiv) at 0 °C over 5–10 min under Ar. The mixture was warmed to 50 °C and stirred for 2–4.5 h. The cooled mixture (ice) was quenched with sat. aq. solution of Rochelle salt and water. Et2O was added and stirred for 2–5 h at RT. The layers were separated and the aqueous phase was extracted with Et2O. The combined organic layers were washed with brine and dried over MgSO4. The solvents were evaporated in vacuo (75 °C, 30 mbar). The crude product was purified either by bulb-to-bulb vacuum distillation (Kugelrohr) or FLC to furnish a corresponding alcohol 20, 22, 23.

3-(But-3-en-2-yl)-2,2-dimethylpropan-1-ol (20)

Ketal 16 (0.5 g, 3.2 mmol), THF (16 mL), 1M DIBAL in toluene (17.4 mL, 17.4 mmol, 5.5 equiv, 7 min), 50 °C, 44 h, sat. aq. Rochelle salt soln. (25 mL), water (5 mL), Et2O (150 mL), 5 h, Et2O (2 × 25 mL), brine (50 mL), bulb-to-bulb vacuum distillation (135–145 °C, 31 mbar), alcohol 20 (307 mg, 61%) as colourless oil; Rf (hexanes/AcOEt 5:1) 0.3; δmax (ATR) 3399 (OH), 2972, 2956, 2870, 1475, 1421, 1368, 1319, 1094, 1044, 991, 921 cm−1; δH (300 MHz, CDCl3) 5.70 (ddd, J = 17.3, 10.3, 7.1 Hz, 1H, CH=CH2), 5.17 (ddd, J = 14.6, 1.6, 1.0 Hz, 1H, CH=CH2), 5.12 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H, CH=CH2), 3.82–3.71 (m, 1H, CH), 3.44 (s, 2H, CH2), 3.34 (d, J = 8.9 Hz, 1H, CH2), 3.16 (d, J = 8.8 Hz, 1H, CH2), 2.91 (brs, 1H, OH), 1.23 (d, J = 6.4 Hz, 3H, Me), 0.91 (s, 6H, Me2); δc (151 MHz, CDCl3) 140.0 (CH=CH2),
115.9 (CH=CH₂), 78.2 (CH₂), 77.8 (CH), 72.4 (CH₂), 35.9 (C₉), 21.9 (Me₂), 21.2 (Me); HR-MS (HESI): M⁺, found 158.1303. C₉H₁₈O₂ requires 158.1301.

2,2-Dimethyl-3-(pent-1-en-3-yloxy)propan-1-ol (22)
Ketal 17 (0.8 g, 4.7 mmol), THF (23.5 mL), 1M DIBAL in toluene (18.6 mL, 18.6 mmol, 4.5 equiv) was added dropwise at 0 °C over 5 min under Ar. The mixture was stirred for 1.10–1.25 equiv) and NaHCO₃ (100%), 185.2 (58, M+H) (m/z 169.2 (100, M-H) (HE) 3411 (OH)), 2961, 2873, 1475, 1422, 1322, 1091, 1045, 993, 921 cm⁻¹; δ₁H (600 MHz, CDCl₃) 5.46 (dd, J = 17.2, 10.5, 7.5 Hz, 1H, CH=CH₂), 5.20–5.14 (m, 2H, CH=CH₂), 3.50 (dd, J = 13.6, 6.7 Hz, 1H, CH), 3.44 (d, J = 5.2 Hz, 2H, OCH₂), 2.38 (d, J = 8.8 Hz, 1H, OCH₂), 3.11 (d, J = 8.8 Hz, 1H, OCH₂), 2.91 (t, J = 5.6 Hz, 1H, OH), 1.63–1.47 (m, 2H, CH₂), 0.93 (s, 3H, Me), 0.90 (s, 3H, Me), 0.90 (t, J = 7.5 Hz, 3H, Me); δC (151 MHz, CDCl₃) 138.6 (CH=CH₂), 116.9 (CH=CH₂), 83.5 (OCH₂), 78.4 (OCH₂), 72.4 (OCH₂), 36.0 (C₉), 28.3 (CH₂), 21.9 (Me₂), 9.6 (Me); HR-MS (HESI): M⁺, found 172.1463. C₁₀H₂₀O₂ requires 172.1458.

3-(Cyclopent-2-enyloxy)-2,2-dimethylpropan-1-ol (23)
Ketal 18 (596 mg, 3.5 mmol), THF (17.7 mL), 1M DIBAL in toluene (10.6 mL, 10.6 mmol, 3 equiv, 10 min), 50 °C, 50 h, sat. aq. Rochelle salt soln. (13 mL), water (60 mL), Et₂O (75 mg) as colourless oil; Rf (hexanes/AcOEt 5:1) 0.29; νmax (ATR) 3419 (OH), 2953, 2854, 1474, 1359, 1116, 1082, 1041 cm⁻¹; δ₁H (600 MHz, CDCl₃) 6.02–5.99 (m, 1H, C=CH), 3.44 (d, J = 8.6 Hz, 1H, OCH), 2.50–2.43 (m, 1H, CH), 2.28–2.22 (m, 1H, CH₂), 2.16–2.09 (m, 1H, CH₂), 1.77–1.70 (m, 1H, CH₂), 0.91 (s, 6H, Me₂); δC (151 MHz, CDCl₃) 135.9 (CH=CH), 130.4 (CH=CH), 85.4 (CH), 78.1 (OCH₂), 72.4 (OCH₂), 35.9 (C₉), 31.0 (CH₂), 29.6 (CH₂), 22.0 (Me₂); m/z (ESI) 169.2 (100, M-H⁺), 170.2 (10, M⁺), tᵣ = 1.96 min; HR-MS (HESI): M⁺, found 170.1312. C₁₀H₁₈O₂ requires 170.1301.

3.2.5. Preparation of Alcohol (24)
To a cooled mixture of ketals 19 + 25 (5:1, 754 mg, 4.1 mmol) in anhydrous THF (20.7 mL) 1M solution of DIBAL in toluene (18.6 mL, 18.6 mmol, 4 equiv) was added dropwise at 0 °C over 5 min under Ar. The mixture was warmed to 50 °C and stirred for 88 h. The cooled mixture (ice) was quenched with sat. aq. soln. of Rochelle salt (30 mL) and water (15 mL), diluted with Et₂O (70 mL) and stirred for 2.5 h at RT. The layers were separated and the aqueous phase was extracted with Et₂O (2 × 35 mL). The combined organic layers were washed with brine (70 mL) and dried over MgSO₄. The solvents were evaporated in vacuo (73 °C, 30 mbar). The crude material was purified by FLC (31 g SiO₂, gradient elution DCM/iPrOH 70:1 (213 mL) → 35:1 (36 mL)) to furnish desired alcohol 24 (303 mg, 48%) and unreacted ketal 25 (75 mg) as colourless oils.
3-(Cyclohex-2-enyloxy)-2,2-dimethylpropanol (24): Rf (DCM/iPrOH 70:1) 0.19; νmax (ATR) 3426 (OH), 3026, 2934, 2865, 1474, 1393, 1080, 1045, 947, 898, 725 cm⁻¹; δ₁H (300 MHz, CDCl₃) 5.84–5.81 (m, 1H, OCH), 5.74 (dd, J = 10.1, 3.5, 1.2 Hz, 1H, CH=CH), 5.46 (dd, J = 10.1, 3.2, 2.0 Hz, 1H, CH=CH), 3.83–3.75 (m, 1H, CH), 3.44 (d, J = 3.8 Hz, 2H, OCH₂), 3.38 (d, J = 8.7 Hz, 1H, OCH₂), 3.33 (d, J = 8.6 Hz, 1H, OCH₂), 2.99 (bs, 1H, OH), 2.10–1.45 (m, 6H, 3 × CH₂), 0.92 (s, 6H, Me₂); δC (151 MHz, CDCl₃) 131.0 (CH=CH), 127.3 (CH=CH), 78.1 (OCH₂), 73.5 (CH), 72.4 (OCH₂), 36.0 (C₉), 28.2 (CH₂), 25.1 (CH₂), 21.9 (Me₂), 19.1 (CH₂); m/z (ESI) 105.2 (100%), 185.2 (58, M+H⁺), 186.2 (10%), tᵣ = 3.13 min; HR-MS (HESI): M⁺, found 184.1445. C₁₁H₂₀O₂ requires 184.1458.

3.2.6. General Experiment for the Preparation of Aldehydes (3–7)
To a solution of alcohol 20–24 in anhydrous DCM Dess–Martin periodinane (DMP, 1.10–1.25 equiv) and NaHCO₃ (0.27 equiv) was added under Ar. The mixture was stirred
for 2–6 h at RT and quenched with sat. aq. NaHCO₃ soln. followed by addition of sat. aq. Na₂S₂O₃ soln. and the stirring continued until all solids dissolved (1–4 h). The layers were separated, the aqueous layer was extracted with DCM and the combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed in vacuo (40 °C, 100–200 mbar) and residue was purified by either FLC or PTLC to furnish corresponding aldehyde 3–7.

3-(But-3-en-2-yloxy)-2,2-dimethylpropan-1-ol (3)

Alcohol 20 (163 mg, 1.03 mmol), DCM (10.3 mL), DMP (546 mg, 1.29 mmol, 1.25 equiv), NaHCO₃ (24 mg, 0.28 mmol), 3 h, sat. aq. NaHCO₃ soln. (8.4 mL), sat. aq. Na₂S₂O₃ soln. (8.4 mL), 1 h, DCM (3 × 25 mL), brine (40 mL), evaporation in vacuo (40 °C, 200 mbar), FLC (8.5 g SiO₂, DCM, 150 mL), aldehyde 3 (62 mg, 38%) as colourless oil; Rₘ (DCM) 0.5: vₘₐₓ (ATR) 2974, 2932, 2871, 1729 (C=O), 1474, 1367, 1092, 992, 925, 910 cm⁻¹; δ₁H (600 MHz, CDCl₃) 9.55 (s, 1H, CHO), 5.68 (ddd, J = 17.3, 10.3, 7.1 Hz, 1H, CH=CH₂), 5.15 (dt, J = 17.2, 1.3 Hz, 1H, CH=CH₂), 5.11 (dt, J = 10.3, 1.4 Hz, 1H, CH=CH₂), 3.78–3.72 (m, 1H, CH₃), 3.46 (d, J = 9.3 Hz, 1H, CH₂), 3.29 (d, J = 9.3 Hz, 1H, CH₂), 1.19 (d, J = 6.4 Hz, 3H, Me), 1.06 (s, 6H, 2 × Me); δC (151 MHz, CDCl₃) 205.7 (CHO), 138.8 (CH=CH₂), 114.5 (CH=CH₂), 130.0 (CH₂), 97.3 (C₆H₅), 73.4 (CH₂), 47.0 (C₆H₅), 21.0 (Me), 19.0 (Me₂); m/z (ESI) 157.2 (26, M⁺ + H), 158.2 (3%), τᵣ = 2.48 min; HR-MS (HESI): M⁺, found 156.1139. C₉H₁₆O₂ requires 156.1145.

2,2-Dimethyl-3-(2-methyl-but-3-en-2-yloxy)propan-1-ol (4)

Alcohol 21 (81 mg, 0.47 mmol), DCM (4.7 mL), DMP (219 mg, 0.52 mmol), NaHCO₃ (11 mg, 0.13 mmol), 2.5 h, sat. aq. NaHCO₃ soln. (3.8 mL), sat. aq. Na₂S₂O₃ soln. (3.8 mL), 1 h, DCM (3 × 12 mL), brine (25 mL), evaporation in vacuo (40 °C, 200 mbar), FLC (6.3 g SiO₂, Hexanes/Et₂O 8:1, 180 mL), aldehyde 4 (31 mg, 39%) as colourless oil; Rₘ (hexanes/Et₂O 8:1) 0.55; vₘₐₓ (ATR) 2976, 1731 (C=O), 1361, 1150, 1080, 1002, 924 cm⁻¹; δ₁H (400 MHz, CDCl₃) 9.52 (s, 1H, CHO), 5.75 (dd, J = 17.8, 10.6 Hz, 1H, CH=CH₂), 5.12 (dd, J = 4.9, 1.2 Hz, 1H, CH=CH₂), 5.08 (dd, J = 2.2, 1.2 Hz, 1H, CH=CH₂), 3.28 (s, 2H, CH₂), 1.22 (s, 6H, 2 × Me), 1.04 (s, 6H, 2 × Me); δC (100 MHz, CDCl₃) 206.1 (CHO), 143.7 (CH=CH₂), 113.9 (CH=CH₂), 74.9 (OC₆H₅), 67.8 (CH₂), 46.7 (C₆H₅), 25.5 (Me₂), 19.0 (Me₂); HR-MS (HESI): M⁺, found 170.1309. C₁₀H₁₆O₂ requires 170.1301.

2,2-Dimethyl-3-(pent-1-en-3-yloxy)propan-1-ol (5)

Alcohol 22 (107 mg, 0.62 mmol), DCM (6.2 mL), DMP (328 mg, 0.77 mmol), NaHCO₃ (14 mg, 0.17 mmol), 3 h, sat. aq. NaHCO₃ soln. (5 mL), sat. aq. Na₂S₂O₃ soln. (5 mL), 1.5 h, DCM (3 × 15 mL), brine (30 mL), evaporation in vacuo (40 °C, 100 mbar), FLC (8.8 g SiO₂, Hexanes/Et₂O 7:1, 80 mL), aldehyde 5 (48 mg, 46%) as colourless oil; Rₘ (hexanes/Et₂O 5:1) 0.61; vₘₐₓ (ATR) 2996, 1731, 1454, 1322, 1092, 924 cm⁻¹; δ₁H (600 MHz, CDCl₃) 9.56 (s, 1H, CHO), 5.62 (ddd, J = 17.0, 10.6, 7.5 Hz, 1H, CH=CH₂), 5.17–5.13 (m, 2H, CH=CH₂), 3.50 (d, J = 9.3 Hz, 1H, OCH₂), 3.51–3.46 (m, 1H, CH), 3.24 (d, J = 9.3 Hz, 1H, OCH₂), 1.59–1.51 (m, 1H, CH₂), 1.50–1.42 (m, 1H, CH₂), 1.07 (s, 6H, 2 × Me), 0.86 (t, J = 7.4 Hz, 3H, Me); δC (151 MHz, CDCl₃) 205.7 (CHO), 138.8 (CH=CH₂), 116.7 (CH=CH₂), 83.4 (CH), 73.7 (OCH₂), 47.2 (C₆H₅), 28.2 (CH₂), 19.0 (Me₂), 9.6 (Me); HR-MS (HESI): M⁺, found 170.1305. C₁₀H₁₄O₂ requires 170.1301.

3-(Cyclopent-2-enyloxy)-2,2-dimethylpropan-1-ol (6)

Alcohol 23 (87 mg, 0.51 mmol), DCM (5.1 mL), DMP (270 mg, 0.64 mmol), NaHCO₃ (12 mg, 0.14 mmol), 2 h, sat. aq. NaHCO₃ soln. (4.2 mL), sat. aq. Na₂S₂O₃ soln. (4.2 mL), 2 h, DCM (3 × 13 mL), brine (30 mL), evaporation in vacuo (40 °C, 200 mbar), PTLC (Hexanes/Et₂O 3:1), aldehyde 6 (19 mg, 22%) as colourless oil; Rₘ (hexanes/Et₂O 3:1) 0.61; vₘₐₓ (ATR) 2931, 2854, 1729 (C=O), 1359, 1116, 1087, 1043, 897, 731 cm⁻¹; δ₁H (600 MHz, CDCl₃) 9.55 (s, 1H, CHO), 6.01–5.98 (m, 1H, CH=CH), 5.82–5.79 (m, 1H, CH=CH), 4.55–4.51 (m, 1H, CH), 3.44 (d, J = 9.2 Hz, 1H, OCH₂), 3.42 (d, J = 9.2 Hz, 1H, OCH₂), 2.48–2.41 (m, 1H, CH₂), 2.28–2.21 (m, 1H, CH₂), 2.14–2.07 (m, 1H, CH₂), 1.75–1.68 (m, 1H, CH₂), 1.07 (s, 6H, 2 × Me); δC
(151 MHz, CDCl$_3$) 205.8 (CHO), 135.7 (CH=CH), 130.5 (CH=CH), 85.4 (CH), 73.3 (OCH$_2$), 47.0 (C$_3$q), 31.1 (CH$_2$), 29.4 (CH$_2$), 19.1 (Me$_2$); HR-MS (HESI): M$^+$, found 168.1141. C$_{10}$H$_{16}$O$_2$ requires 168.1145.

3-(Cyclohex-2-enyloxy)-2,2-dimethylpropan-1-al (7)

Alcohol 24 (150 mg, 0.81 mmol), DCM (8.1 mL), DMP (432 mg, 1.02 mmol), NaHCO$_3$ (19 mg, 0.23 mmol), 5.5 h, sat. aq. NaHCO$_3$ soln. (6.6 mL), sat. aq. Na$_2$S$_2$O$_3$ soln. (6.6 mL), 3.5 h, DCM (3 × 20 mL), brine (30 mL), evaporation in vacuo (40 °C, 100 mbar), FLC (7.9 g SiO$_2$, DCM, 180 mL), aldehyde 7 (89 mg, 60%) as colourless oil; R$_f$ (DCM) 0.56; $\nu_{\text{max}}$ (ATR) 2933, 2865, 1729 (C=O), 1474, 1395, 1084, 948, 895, 726 cm$^{-1}$; $\delta$H (600 MHz, CDCl$_3$) 9.57 (s, 1H, CHO), 5.85–5.81 (m, 1H, C=CH), 5.73–5.69 (m, 1H, CH=C), 3.82–3.77 (m, 1H, OCH$_2$), 3.50 (d, $J$ = 9.1 Hz, 1H, OCH$_2$), 2.06–1.99 (m, 1H, CH$_2$), 1.97–1.90 (m, 1H, CH$_2$), 1.82–1.76 (m, 1H, CH$_2$), 1.75–1.68 (m, 1H, CH$_2$), 1.65–1.58 (m, 1H, CH$_2$), 1.55–1.48 (m, 1H, CH$_2$), 1.08 (s, 3H, Me), 1.07 (s, 3H, Me); $\delta$C (151 MHz, CDCl$_3$) 205.8 (CHO), 130.8 (CH=CH), 127.5 (CH=CH), 73.6 (CH), 73.3 (OCH$_2$), 47.1 (C$_3$q), 28.1 (CH$_2$), 25.2 (CH$_2$), 19.2 (CH$_2$), 19.1 (Me$_2$); HR-MS (HESI): M$^+$, found 182.1302. C$_{11}$H$_{18}$O$_2$ requires 182.1301.

4. Conclusions

We have designed, synthesised, and evaluated a set of new (racemic) seco-analogues 3–7 of lilac aldehydes featuring a higher conformational freedom and/or variable substitution pattern of the alkene moiety. Thus, starting from commercially available α-chloroketones 8–11, we have prepared target aldehydes from intermediary alcohols 20–24 via the reductive ring-opening of respective ketals 16–19. The qualitative olfactory analysis of novel seco-analogues 3–7 revealed that the opening of tetrahydrofuran ring leads to a vanishing of flowery scent typical for lilac aldehydes 1, suggesting the important osmophoric role of THF moiety in these natural products. Moreover, while the ring-opened analogues 3–5 bearing an acyclic alkene exhibit a rather common spicy aroma with green notes, the scent of their congeners featuring a cyclic alkene is further shifted towards fruity aspects for 6 and herbal notes for 7. For comparison purposes, we have also included alcohols 20–24 in the olfactory screening. Interestingly, while the respective alcohols 20, 22, 23, and 24 commonly exhibit sweet aroma with fatty and turpentine-like facets, alcohol 21 features a pleasant balsamic aroma with minty-eucalyptus notes. However, the aroma intensity for all compounds was weak to moderate with only short persistence over time.

Supplementary Materials: The copies of NMR spectra of new compounds are available online.

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