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Volatiles from the ascomycete *Daldinia cf. childiae* (Hypoxylaceae), originating from China†

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The volatiles from an isolate of the fungus *Daldinia cf. childiae*, obtained from a specimen collected in China, were collected by use of a closed-loop stripping apparatus and analysed by GC-MS. A total number of 33 compounds from different classes were rigorously identified by comparison of mass spectra to library spectra and of retention indices to tabulated data from the literature. For unknown compounds structural suggestions were delineated from the mass spectra and verified by chemical synthesis of reference materials. Through this approach two 2-alkylated furan derivatives were identified, demonstrating that the genus *Daldinia* continues to be an interesting source for the discovery of novel secondary metabolites. Feeding experiments with sodium (1,2-¹³C₂)acetate were performed to investigate the biosynthesis of the polyketide 5-hydroxy-2-methyl-4-chromanone that are in favour of a non-enzymatic cyclisation step.

Introduction

The Xylariales are an order of mostly saprophytic ascomycete fungi that grow on decaying wood. They are rich producers not only of volatile secondary metabolites,¹ but also of larger polyoxygenated natural products from diverse compound classes that often exhibit interesting biological activities.² One of the first characterised xylarialean volatile compounds (Fig. 1A) is 2-butyl-3-methylbut-2-en-4-olide (1) from *Hypoxylon serpens* (currently valid name: *Nemania serpens*),³ a compound that was also found in an endophytic isolate assigned to the genus *Geniculosporium* (the asexual state of *Nemania*).⁴ In *N. serpens* it is accompanied by its isomer 2-butyl-3-methylenbutan-4-olide (2).³ With respect to terpenes, 1,8-cineol (3) has been reported from endophytic species of the genus *Hypoxylon*,^{5,6} and the monoterpene synthase for this compound has recently been identified.⁷ Among non-volatile secondary metabolites compounds (Fig. 1B) from many classes can be found, such as the xylariterpenoids A (4a) and B (4b),⁸ or the daldinones as represented by daldinone A (5a)⁹ and daldionin (5b) that exhibits moderate antimicrobial activity against Gram-positive bacteria.¹⁰ Daldinone A was initially obtained as a minor metabolite from the fruiting bodies of *Daldinia concentrica*, but it is also present in other Hypoxylaceae, e.g. it is extremely frequent in *Annulohypoxylon* where it constitutes the major stromatal pigments of many species.¹¹ Following our continuous effort in the identification of volatile secondary metabolites from fungi,

Daldinia cf. childiae MUCL 53761, a species isolated from China,¹² came into our focus. The strain had already been included in a study containing preliminary data on its GC-MS profile, but the main focus of this study was on the discovery and description of the new species *Daldinia hawksworthii*.¹³ The bouquet of *D. cf. childiae* was found to contain several natural products that could not be easily identified from their mass spectra. Here we report on a re-investigation of the volatiles from *D. cf. childiae* with a special emphasis on the extended chemical space observed in this organism.

Results and discussion

Headspace analysis

The volatile organic compounds emitted by agar plate cultures of *Daldinia cf. childiae* were collected on charcoal filters

Fig. 1 Secondary metabolites from Xylariales. The figure shows examples for A) volatile and B) non-volatile compounds.

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with a closed-loop stripping apparatus (CLSA) as described by Grob and Zürcher.¹⁴ After one day the trapped compounds were extracted with dichloromethane and the obtained headspace extracts were analysed by gas chromatography-mass spectrometry (GC-MS). The detected compounds were identified from their mass spectra by comparison to mass spectral libraries, and from their retention indices¹⁵ by comparison to literature data for the same (HP5-MS) or similar GC column type of same polarity (polydimethylsiloxane coating with 5% phenyl groups). Positive compound identification was assumed for a good mass spectral match and deviation between measured and reported retention index of no more than 10 points. If library mass spectra or retention index literature data were not available, an authentic reference compound was used for unambiguous compound identification. As will be reported here, for a few compounds that were not commercially available structural suggestions were made based on the recorded mass spectral fragmentation patterns and the chromatographic behaviour. The structural suggestions were then verified or disproven by synthesis of a reference compound.

Identification of volatiles from *Daldinia cf. childiae*

A total number of 33 different compounds representing various compound classes were identified in the headspace extracts from *D. cf. childiae* (Fig. 2 and 3, Table S1†) including the biosynthetically related aliphatic compounds 4-methylhexan-3-one (6), manicone (7) and (4*R*,5*R*,6*S*)-5-hydroxy-4,6-dimethyloctan-3-one (8). The absolute configuration of compound 8 was recently determined for the same compound produced by *Daldinia clavata* by comparison to all eight synthetic stereoisomers through GC using a chiral stationary phase.¹⁶ Furthermore, the widespread typical mushroom odour oct-1-en-3-ol (9, matsutake alcohol) and traces of cyclohexanol (10) and cyclohexanone (11) were detected.

Small heterocyclic compounds were represented by 2-acetylfuran (12), 2-acetylthiazole (13), 2,5-dimethylpyrazine (14) and 2,4,6-trimethylpyridine (15). While 12–14 are widespread volatiles, compound 15 is rare and has only occasion-

Fig. 3 Volatiles from *Daldinia cf. childiae*. The absolute configuration of compounds 6, 7, 9 and 16 is unknown.

Fig. 2 Total ion chromatogram of a CLSA headspace extract from *Daldinia cf. childiae* MUCL 53761. The bold compound numbers at peaks correspond to those in Table S1† and in Fig. 3.

ally been reported as a constituent of plant essential oils^{17–19} and from bacteria of the genus *Collimonas*,²⁰ but never from fungal sources before. Aromatic compounds included the widespread volatiles 2-phenylethanol (18), its isomer 1-phenylethanol (16) and the corresponding ketone acetophenone (17).

The main volatile 5-hydroxy-2-methyl-4-chromanone (22) from *D. cf. childiae* was also found in liquid culture extracts and isolated for unambiguous identification by NMR spectroscopy (Fig. S1–S3†). The chromanone 22 is a small polyketide that was first reported from the plant pathogenic fungus *Phialophora gregata*²¹ and is also known from other species of the genus *Daldinia*^{22,23} and the related genera *Thamnomycetes*²⁴ and *Phylacia*.²⁵ Its optical rotation of $[\alpha]_D^{20} =$

-0.1 (c 1.6, CH_2Cl_2) pointed to a racemic sample, as verified by GC on a chiral stationary phase (Fig. S4†), while for **22** from *Nodulisporium* a slight enrichment of the (*R*) enantiomer was reported ($[\alpha]_{\text{D}}^{25} = +6$, c 0.19, CH_2Cl_2 , 6% ee for (*R*)-**22**).²⁶ The corresponding compounds 2-methyl-4-chromanone (**21**) and 5-hydroxy-2-methyl-4*H*-chromen-4-one (**23**) were also detected as minor constituents. The polyketide synthase ChrA for chromane biosynthesis was recently reported from *Daldinia eschscholtzii* and acts together with a discrete keto-reductase ChrB (Scheme 1).²⁷

The biosynthetic model for the main compound **22** (Scheme 1A) includes the formation of a pentaketide chain from an acetyl-CoA starter unit and malonyl-CoA extender units with ketoreduction and elimination of water during the first chain extension step. Reduction of the 3-oxo group of the ACP-bound pentaketide by the ketoreductase ChrB and cyclisation by Dieckmann condensation leads to 1-(2,6-dihydroxyphenyl)but-2-en-1-one (**34**) that can undergo spontaneous cyclisation to **22**. The minor compound **23** is similarly formed from a pentaketide in which only the 3-oxo group is reduced to the alcohol, followed by cyclisation to 1-(2,6-dihydroxyphenyl)butane-1,3-dione (**36**) and spontaneous formation of the hemiacetal **37** and elimination of water to **23** (Scheme 1B). This biosynthetic model was supported by a feeding experiment with sodium (1,2-¹³C₂)acetate, resulting in a good incorporation of labelling (14% incorporation rate)

and up to five labelled C₂ units (Fig. S5†). The coupling pattern in the ¹³C-NMR spectrum of labelled **22** (Fig. 4) demonstrates that the labelled acetate units in the pseudosymmetric aromatic ring are oriented in a clockwise (C-4a/C-8a, C-8/C-7 and C-6/C-5) or counterclockwise arrangement (C-4a/C-5, C-6/C-7 and C-8/C-8a) which is explainable by the C_{2v} symmetric intermediate **34**. The equal peak integrals for both coupling patterns also suggest that the conversion from **34** to **22** is likely not under control of the PKS or any other enzyme, which is also reflected by the racemic nature of **22**. Liquid culture extracts also yielded 1-(2,6-dihydroxyphenyl)butan-1-one (**35**, Fig. S6–S8†), a compound that was previously reported *inter alia* from an endophytic *Nodulisporium* and *D. eschscholtzii*,^{10,23,28} whose formation can be explained by full reduction in the first PKS extension step. This compound was neither present in the headspace nor the liquid culture extracts from the feeding experiment with sodium (1,2-¹³C₂)acetate.

The compounds **36** and **37** have also previously been reported from *Daldinia*,²⁹ which further supports the biosynthetic hypothesis. The methyl esters methyl salicylate (**19**) and methyl 2,6-dihydroxybenzoate (**20**) found in the headspace extracts exhibit the same aromatic ring substitution patterns as observed for **21** and **22** and may arise by degradation of these chromanones. An alternative biosynthetic hypothesis in which the coenzyme A esters of salicylic acid and 2,6-

Scheme 1 Chromanone biosynthesis in *Daldinia* by the partially reducing polyketide synthase (PR-PKS) ChrA in conjunction with the discrete ketoreductase ChrB. Biosynthetic models for A) 5-hydroxy-2-methyl-4-chromanone (**22**) and B) 5-hydroxy-2-methyl-4*H*-chromen-4-one (**23**). ACP: acyl carrier protein, AT: acyl transferase, DH: dehydratase, KR: ketoreductase, KS: ketosynthase, MT: methyltransferase.

Fig. 4 Expansions of the ^{13}C -signals for all carbons of labelled **22** obtained in the feeding experiment with sodium $(1,2\text{-}^{13}\text{C}_2)$ acetate. The intact labelled C_2 units are shown as bold arrows in different colours. The corresponding ^{13}C , ^{13}C couplings are indicated in the ^{13}C -spectra by the same colour. The coupling pattern in the aromatic ring can be explained by either clockwise or counterclockwise incorporation of labelled C_2 units.

dihydroxybenzoic acid would serve as starter units (Scheme S1†) is excluded by the observed incorporation pattern from sodium $(1,2\text{-}^{13}\text{C}_2)$ acetate, because for this alternative mechanism the C-2/C-3 unit of **22** should arise from one acetate.

The second most abundant volatile from *D. clutidae* was identified as 1,8-dimethoxynaphthalene (**24**). This compound has been previously reported from other fungi including *D. eschscholtzii*,³⁰ *Hypoxylon invadens*³¹ and *Hypoxylon*

*griseobrunneum*³² that all belong to the family Hypoxylaceae.³³ The corresponding compound 1,8-dihydroxynaphthalene (1,8-DHN), which is likely the biosynthetic precursor of **24**, also serves as a building block of 1,8-DHN melanin in ascomycota.³⁴

For compounds **25** and **26** no reference mass spectra were included in our mass spectral libraries, but the fragmentation pattern pointed to the structures of 2-alkylated furans by the strong fragment ions at $m/z = 81$ and 95 , representing the furan moiety by α - and β -cleavage (Fig. 5A and B). Together with the molecular ions at $m/z = 194$ and 222 the structures of 2-nonylfuran (**25**) and 2-undecylfuran (**26**) were suggested. Both compounds were synthesised by alkylation of furan with the corresponding alkyl halogenides **38** and **39** (Scheme 2, for NMR spectra cf. Fig. S9–S14†). The obtained products showed identical mass spectra and retention times to the volatiles from *D. cf. childiae*, thus giving unambiguous evidence for the suggested structures. 2-Nonylfuran has been reported as an essential oil constituent of *Bifora radians*,³⁵ while 2-undecylfuran is known from tonka beans (*Dipteryx odorata*),³⁶ but both compounds have not been described as a fungal natural product before.

Two more trace compounds **X** and **Y** eluted slightly later than **25** and **26** and showed very similar mass spectra, but the molecular ions were 2 Da lower with $m/z = 192$ and 220 , suggesting an additional unsaturation in the side chain (Fig. 5C and D). It is difficult to determine the positions of double bonds in long alkenyl chains from mass spectral fragmentation patterns. To solve this problem the iodine catalysed addition of dimethyl disulfide to olefins is often used.³⁷ This method yields bis(methylthio) ethers that show strong α -fragmentations of the chain between the thioether groups, but the production of **X** and **Y** was too low for derivatisations in microreactions. Biosynthetically, the furans may arise from fatty acids, and for this reason we assumed that the double bond for **X** may be located in the ω -6 position and **Z** configured as in linolenic acid. However, synthetic (*Z*)-2-(non-3-en-1-yl)furan (**41**) prepared by alkylation of furan with (*Z*)-1-iodonon-3-ene (**40**) showed a different mass spectrum and retention index than **X** (Fig. S15,† NMR spectra are shown in Fig. S16–S18†). As an alternative, 2-(non-1-en-1-yl)furan (**45**) and 2-(undec-1-en-1-yl)furan (**46**), compounds that can be expected to elute later than **25** and **26**, respectively, due to their conjugated double bond systems, were prepared by Wittig reaction of furfural (**42**) with octyl and decyltriphenylphosphonium salts (**43** and **44**). These reactions yielded the *Z* stereoisomers as the main products along with minor amounts of the *E* isomers, but also these furans exhibited different mass spectra and retention indices than **X** and **Y** (Fig. S15,† for NMR spectra cf. Fig. S19–S24†). The structures of **X** and **Y** remain currently unclear and their identification will require the synthesis of further reference compounds or isolation from culture extracts.

6-Heptyl-2H-pyran-2-one (**27**), known as a volatile organic compound from *Trichoderma viride*,³⁸ was also found in trace amounts. Significantly larger amounts were observed for

Fig. 5 EI mass spectra of A) 2-nonylfuran (**25**) and B) 2-undecylfuran (**26**), and the unidentified furan derivatives with unsaturated side chains C) **X** and D) **Y**.

6-nonyl-2*H*-pyran-2-one (**28**), a compound that we have recently reported from *D. clavata*.¹⁶ Furthermore, a few terpenes were found including the widespread trisnor-sesquiterpene geosmin (**29**),^{1,39} β -bisabolene (**30**), *trans*- β -bergamotene (**31**), and *cis*- and *trans*-linalool oxide (**32** and **33**). The sesquiterpenes **30** and **31** are biosynthetically linked through the bisaboyl cation **A** (Scheme 3) and may potentially arise from the same sesquiterpene synthase. Notably,

Scheme 2 Synthesis of 2-alkyl and 2-alkenylfurans.

Scheme 3 Cyclisation of farnesyl diphosphate (FPP) via nerolidyl diphosphate (NPP) and the bisaboyl cation (**A**) as last common intermediate towards **30** and **31**.

the combination of **30** and **31** has recently also been reported from *Aspergillus fischeri*.⁴⁰

Conclusions

The previous study of the same strain had tentatively revealed compounds like 5-methoxy-1,3-dimethyl-1*H*-pyrazole, 7-methoxy-1-naphthol, guaia-1(10),11-diene, 5-ethyl-4-methylhept-4-en-3-one, and 6,6-dimethylhepta-1,3-dien-5-ol as major detectable metabolites, but only with poor mass spectral accordance values of *ca.* 60% according to the NIST database

and without a comparison of retention indices.¹³ Moreover, the chromane (23) was detected with confidence as a major metabolite, relying on an available standard. The fact that none of the above mentioned compounds except for 23 was confirmed to be present in the volatilome of the fungus during the course of the current study should give rise to take such preliminary data more cautiously, because only a relatively small number of volatiles derived from fungi are contained in the NIST database. On the other hand, the current work shows that it may be rewarding to study fungi more intensively with the goal of obtaining new fungal volatiles with potentially interesting functions in fungal ecology. The profile of fungal volatiles is also interesting, because the presence of some compounds may point to the production of functionalised non-volatile metabolites with interesting medicinal properties, e.g. *trans*- β -bergamotene (31) is the parent hydrocarbon of the xylariterpenoids A (4a) and B (4b), and 1,8-dimethoxynaphthalene (24) is biosynthetically linked to the pseudo-dimeric structures of daldinones such as 5a and daldionin (5b). In future studies we will continue to investigate the interesting chemical space of fungal volatiles.

Experimental part

Strain and culture conditions

The culture of *Daldinia cf. childiae* was originally obtained from ascospores of a specimen that was collected by Cony Decock in China (Yunnan Province, Chu Xiong, Zi Xi Shan Nature Reserve) from *Prunus* on 17 September 2008, and is deposited at the Mycothèque de l' Université Catholique de Louvain (BCCM/MUCL), Louvain-la-Neuve (Belgium), under the accession number MUCL 53761. Its taxonomy has been previously reported in the course of the last world monograph of the genus *Daldinia*.¹² The specimen showed a highly similar morphology as compared to *Daldinia childiae*, but differed from typical material of this extremely frequently occurring species in having a deviating stromatal morphology and slightly larger ascospores with aberrant germ slit morphology. Its anamorphic characteristics and HPLC profile were the same as in *D. childiae* from other localities, and the ITS sequence also did not deviate. For these reasons, and because only a single specimen has so far become available, the fungus has not yet been formally assigned to a new species. The strain was grown in YMG liquid medium (4 g L⁻¹ yeast extract, 10 g L⁻¹ malt extract, 4 g L⁻¹ glucose, pH 7.2) at 25 °C with agitation or on YMG agar plates.

Analysis of volatiles

The volatiles released by *Daldinia cf. childiae* MUCL 53761 agar plate cultures were trapped on charcoal filters using a closed-loop stripping apparatus (CLSA) as described by Grob and Zürcher¹⁴ for 24 h at room temperature with natural light-dark rhythm. The adsorbed volatiles were extracted from the filter traps with CH₂Cl₂ (50 μ L, HPLC grade) and the obtained extracts were subjected to GC/MS analysis.

GC/MS

GC/MS analyses were carried out with a coupled 7890A GC – 5975C mass selective detector system (Agilent, Hewlett-Packard Company, Wilmington, USA). The GC was equipped with a HP5-MS fused silica capillary column (30 m, 0.25 mm i. d., 0.25 μ m film, Agilent). The GC/MS settings were inlet pressure: 77.1 kPa, He 23.3 mL min⁻¹; injection volume: 1.5 μ L; injector operation mode: splitless (60 s valve time); carrier gas: He at 1.2 mL min⁻¹; GC program: 5 min at 50 °C, then increasing with 5 °C min⁻¹ to 320 °C; transfer line 300 °C; electron energy 70 eV. Retention indices (*I*) were calculated according to Kovats¹⁵ from retention times of the analytes in comparison to those of alkane standards in a homologous series of *n*-alkanes (C₈–C₃₈).

GC on chiral stationary phase

The enantiomeric composition of 22 was determined on an Agilent 7820A GC system equipped with an FID detector and a Cyclosil B column (30 m, 0.25 mm diameter, 0.25 μ m film). The GC was programmed as follows: start temperature 110 °C, held for 5 min, followed by a temperature ramp of 40 °C min⁻¹ to 130 °C, then a ramp of 2.5 °C min⁻¹ to 220 °C. Inlet temperature: 250 °C, injection volume: 1 μ L, carrier gas: H₂, gas flow: 2.3 mL min⁻¹.

Compound isolation from liquid culture extracts

Daldinia cf. childiae MUCL 53761 was grown in YMG liquid medium (6 L) for two days. After centrifugation the supernatant was extracted with diethyl ether (3 $\times$). The combined organic layers were dried with MgSO₄ and concentrated under reduced pressure to yield the crude extract (0.4 g). Column chromatography on silica gel with diethyl ether/pentane (5 : 1) yielded two fractions (F1 and F2). Fraction F1 was further purified by a second column chromatography on silica gel with diethyl ether/pentane (1 : 5) to yield pure 22 (15 mg) as a colourless oil and five fractions (F1.1–F1.5). Fraction 1.2 was purified by preparative TLC (silica gel, toluene/ethyl acetate 10 : 1) to give pure 35 (7.4 mg) as a colourless oil.

5-Hydroxy-2-methyl-4-chromanone (22). TLC (pentane/diethyl ether 5 : 1): *R*_f = 0.4. ¹H NMR (700 MHz, C₆D₆): δ = 12.35 (br s, 1H, OH), 6.91 (dd, ³*J*_{H,H} = 8.3, 8.3 Hz, 1H, CH), 6.51 (dd, ³*J*_{H,H} = 8.3 Hz, ⁴*J*_{H,H} = 0.9 Hz, 1H, CH), 6.30 (dd, ³*J*_{H,H} = 8.2 Hz, ⁴*J*_{H,H} = 0.9 Hz, 1H, CH), 3.68 (ddq, ³*J*_{H,H} = 9.9, 6.2, 6.2 Hz, 1H, CH), 1.94–1.89 (m, 2H, CH₂), 0.83 (d, ³*J*_{H,H} = 6.3 Hz, 3H, CH₃) ppm. ¹³C NMR (175 MHz, C₆D₆): δ = 198.5 (CO), 163.1 (C_q), 162.1 (C_q), 138.2 (CH), 109.5 (CH), 108.5 (C_q), 107.2 (CH), 73.6 (CH), 43.4 (CH₂), 20.4 (CH₃) ppm. HR-APCI-MS: calcd. for C₁₀H₁₁O₃⁺ 179.0703; found 179.0702. IR (ATR): ν /cm = 2980 (w), 1646 (s), 1627 (m), 1579 (m), 1388 (s), 1349 (m), 1226 (s), 1161 (w), 1147 (w), 1111 (w), 1060 (m), 1012 (w), 939 (w), 903 (w), 870 (w), 801 (m), 730 (m), 578 (w) cm⁻¹. UV-vis (CH₂Cl₂): λ _{max} (log ϵ) = 351 (3.28), 270 (3.66), 227 (3.59), 202 (3.86) nm.

1-(2,6-Dihydroxyphenyl)butan-1-one (35). TLC (pentane/diethyl ether 2 : 1): *R*_f = 0.35. ¹H NMR (700 MHz, C₆D₆): δ =

9.05 (br s, 2H, 2 × OH), 6.78 (t, $^3J_{\text{H,H}} = 8.2$ Hz, 1H, CH), 5.97 (d, $^3J_{\text{H,H}} = 8.1$ Hz, 2H, 2 × CH), 2.86 (t, $^3J_{\text{H,H}} = 7.2$ Hz, 2H, CH₂), 1.65 (tq, $^3J_{\text{H,H}} = 7.3$ Hz, 2H, CH₂), 0.86 (t, $^3J_{\text{H,H}} = 7.4$ Hz, 3H, CH₃) ppm. ^{13}C NMR (175 MHz, C₆D₆): $\delta = 207.2$ (CO), 161.8 (C_q), 135.4 (2 × CH), 110.5 (C_q), 108.5 (2 × CH), 46.7 (CH₂), 18.0 (CH₂), 14.0 (CH₃) ppm. HR-APCI-MS: calcd. for C₁₀H₁₃O₃⁺ 181.0859; found 181.0859. IR (ATR): $\nu/\text{cm}^{-1} = 3276$ (w), 2962 (w), 2929 (w), 2873 (w), 1628 (m), 1586 (s), 1510 (w), 1448 (s), 1385 (w), 1356 (w), 1339 (w), 1297 (w), 1234 (m), 1214 (s), 1196 (s), 1165 (w), 1106 (w), 1037 (m), 980 (m), 901 (w), 871 (w), 794 (m), 725 (m), 595 (w), 534 (w) cm⁻¹. UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 254 (4.93), 212 (4.93) nm.

Feeding experiment with sodium (1,2-¹³C₂)acetate

Daldinia cf. childiae MUCL 53761 was grown in YMG liquid medium (250 mL) supplemented with sodium (1,2-¹³C₂)acetate (210 mg, 2.5 mmol, 10 mM) for two days. After centrifugation the supernatant was extracted with diethyl ether (3×). The combined organic layers were dried with MgSO₄ and concentrated under reduced pressure to yield the crude extract that was directly analysed by NMR spectroscopy.

General synthetic methods

Starting materials were obtained from commercial suppliers (Thermo Fisher Scientific, Waltham, USA; Sigma Aldrich, St. Louis, USA or TCI, Tokyo, Japan) and used without purification. Flash column chromatography was performed on silica (Geduran Si 60, 40–63 μm , Merck, Darmstadt, Germany). Solvents for column chromatography were distilled prior to use. All reactions were carried out in flame dried glassware under Ar atmosphere in solvents dried by standard procedures. All reactions and chromatographic steps were monitored by TLC (silica, Polygram SIL G/UV254, Macherey-Nagel, Düren, Germany). Phosphomolybdic acid in EtOH (10 g/100 mL) was used for staining. NMR spectra were recorded on Bruker instruments (Billerica, USA), Avance III HD Prodigy (500 MHz) or Avance III HD Cryo (700 MHz). Spectra were referenced against solvent signals (^1H -NMR, residual proton signals: CDCl₃ $\delta = 7.26$ ppm, C₆D₆ $\delta = 7.16$ ppm; ^{13}C -NMR: CDCl₃ $\delta = 77.16$ ppm, C₆D₆ $\delta = 128.06$ ppm). Optical rotations were recorded on a P8000 Polarimeter (Krüss Optronic, Hamburg, Germany). IR spectra were measured with a Bruker Alpha FT-IR spectrometer. The intensities of the peaks were assigned as s (strong), m (medium), and w (weak). UV/Vis spectra were recorded on a Cary 100 UV/Vis spectrometer (Agilent).

Synthesis of 2-alkyl and 2-alkenylfurans by alkylation of furan

To a solution of furan (1 eq.) in anhydrous THF (3 mL mmol⁻¹ of furan), a solution of *n*-BuLi (1.6 M in hexane, 1 eq.) was added dropwise at –78 °C, followed by stirring for 30 minutes. Then, a solution of the corresponding alkyl or alkenyl halogenide (1 eq.) in dry THF (0.3 mL mmol⁻¹ of alkyl or alkenyl halogenide) was added. The mixture was stirred at room temperature for another 3 hours. Distilled water was

added and the aqueous layer was extracted with diethyl ether (3×). The collected organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to yield the 2-alkyl and 2-alkenylfurans as colourless oils.

2-Nonylfuran (25). Prepared from nonyl bromide (38, 1.51 g, 7.3 mmol). Yield: 757 mg (3.90 mmol, 53%). TLC (hexane): $R_f = 0.51$. ^1H NMR (400 MHz, CDCl₃, TMS): $\delta = 7.30$ (dd, $^3J_{\text{H,H}} = 1.9$ Hz, $^4J_{\text{H,H}} = 0.9$ Hz, 1H, CH), 6.28 (dd, $^3J_{\text{H,H}} = 1.9$, 3.1 Hz, 1H, CH), 5.97 (m, 1H, CH), 2.62 (t, $^3J_{\text{H,H}} = 7.6$ Hz, 2H, CH₂), 1.64 (m, 2H, CH₂), 1.39–1.22 (m, 12H, 6 × CH₂), 0.89 (t, $^3J_{\text{H,H}} = 6.6$ Hz, 3H, CH₃) ppm. ^{13}C NMR (100 MHz, CDCl₃, TMS): $\delta = 156.7$ (C_q), 140.6 (CH), 110.0 (CH), 104.5 (CH), 31.9 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 28.1 (CH₂), 28.0 (CH₂), 22.7 (CH₂), 14.1 (CH₃) ppm. HR-ESI-MS: calcd. for C₁₃H₂₂O⁺ 194.1665; found 194.1667. IR (ATR): $\nu/\text{cm}^{-1} = 2924$ (m), 2854 (m), 1597 (w), 1507 (w), 1464 (w), 1379 (w), 1146 (w), 1077 (w), 1006 (w), 924 (w), 885 (w), 794 (w), 723 (s), 599 (w) cm⁻¹. UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 277 (2.85), 229 (4.56) nm.

2-Undecylfuran (26). Prepared from undecyl iodide (39, 680 mg, 2.5 mmol). Yield: 150 mg (0.65 mmol, 26%). TLC (cyclohexane): $R_f = 0.90$. ^1H NMR (500 MHz, CDCl₃): $\delta = 7.29$ (dd, $^3J_{\text{H,H}} = 1.6$ Hz, $^4J_{\text{H,H}} = 0.6$ Hz, 1H, CH), 6.27 (dd, $^3J_{\text{H,H}} = 1.9$, 3.1 Hz, 1H, CH), 5.97 (dd, $^3J_{\text{H,H}} = 3.1$ Hz, $^4J_{\text{H,H}} = 0.7$ Hz, 1H, CH), 2.61 (t, $^3J_{\text{H,H}} = 7.6$ Hz, 2H, CH₂), 1.63 (m, 2H, CH₂), 1.37–1.22 (m, 16H, 8 × CH₂), 0.88 (t, $^3J_{\text{H,H}} = 6.9$ Hz, 3H, CH₃) ppm. ^{13}C NMR (125 MHz, CDCl₃): $\delta = 156.7$ (C_q), 140.6 (CH), 110.0 (CH), 104.5 (CH), 32.0 (CH₂), 29.69 (CH₂), 29.67 (CH₂), 29.60 (CH₂), 29.42 (CH₂), 29.39 (CH₂), 29.2 (CH₂), 28.1 (CH₂), 28.0 (CH₂), 22.7 (CH₂), 14.2 (CH₃) ppm. HR-APCI-MS: calcd. for C₁₅H₂₇O⁺ 223.2056; found 223.2056. IR (ATR): $\nu/\text{cm}^{-1} = 2924$ (s), 2854 (s), 1597 (w), 1508 (w), 1466 (w), 1376 (w), 1229 (w), 1216 (w), 1008 (w), 794 (w), 725 (m), 599 (w) cm⁻¹. UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 213 (3.81) nm.

(Z)-2-(Non-3-en-1-yl)furan (41). Prepared from (Z)-1-iodonon-3-ene (40, 0.63 g, 2.50 mmol). Yield: 134 mg (0.70 mmol, 28%). TLC (cyclohexane): $R_f = 0.85$. ^1H NMR (500 MHz, CDCl₃): $\delta = 7.30$ (dd, $^3J_{\text{H,H}} = 1.8$ Hz, $^4J_{\text{H,H}} = 0.8$ Hz, 1H, CH), 6.28 (dd, $^3J_{\text{H,H}} = 3.1$, 1.9 Hz, 1H, CH), 5.99 (dd, $^3J_{\text{H,H}} = 3.1$ Hz, $^4J_{\text{H,H}} = 0.9$ Hz, 1H, CH), 5.45–5.35 (m, 2H, 2 × CH), 2.67 (t, $^3J_{\text{H,H}} = 7.5$ Hz, 2H, CH₂), 2.41–2.36 (m, 2H, CH₂), 2.01 (dt, 2H, $^3J_{\text{H,H}} = 6.8$ Hz, 2H, CH₂), 1.36–1.23 (m, 6H, 3 × CH₂), 0.89 (t, $^3J_{\text{H,H}} = 7.0$ Hz, 3H, CH₃) ppm. ^{13}C NMR (125 MHz, CDCl₃): $\delta = 155.9$ (C_q), 140.8 (CH), 131.1 (CH), 128.1 (CH), 110.1 (CH), 104.9 (CH), 31.5 (CH₂), 29.3 (CH₂), 28.2 (CH₂), 27.2 (CH₂), 25.8 (CH₂), 22.6 (CH₂), 14.1 (CH₃) ppm. HR-APCI-MS: calcd. for C₁₃H₂₁O⁺ 193.1587; found 193.1587. IR (ATR): $\nu/\text{cm}^{-1} = 3008$ (w), 2957 (s), 2926 (s), 2857 (s), 1799 (w), 1597 (w), 1507 (w), 1458 (w), 1261 (w), 1147 (w), 1104 (w), 1078 (w), 1009 (m), 923 (w), 797 (w), 727 (m), 599 (w) cm⁻¹. UV-vis (CH₂Cl₂): λ_{max} (log ϵ) = 214 (3.92) nm.

Synthesis of 2-(alk-1-en-1-yl)furans by Wittig reaction

To a solution of alkyltriphenylphosphonium halide (1.0 eq.) in anhydrous THF (5 mL mmol⁻¹ of halide), a solution of *n*-BuLi

(1.6 M in hexanes, 1.0 eq.) was added dropwise at $-35\text{ }^{\circ}\text{C}$. The red ylide mixture was stirred for 30 minutes followed by dropwise addition of 2-furaldehyde (1.0 eq.) in anhydrous THF (4 mL mmol^{-1} of aldehyde). The mixture was warmed to room temperature overnight. Distilled water was added and the aqueous phase was extracted with ethyl acetate (3 $\times$). The combined organic phases were dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2 , cyclohexane) to yield 2-(alk-1-en-1-yl)furan as yellow oils.

2-(Non-1-en-1-yl)furan (45). Prepared from octyltriphenylphosphonium bromide (**43**, 1.1 g, 2.42 mmol). Yield: 407 mg (2.11 mmol, 88%, *Z/E* 7:1). TLC (cyclohexane): $R_f = 0.80$. ^1H NMR (700 MHz, CDCl_3): $\delta = 7.37$ (d, $^3J_{\text{H,H}} = 1.7$ Hz, 1H, CH, *Z* isomer), 7.30 (d, $^3J_{\text{H,H}} = 1.7$ Hz, 1H, CH, *E* isomer), 6.39 (dd, $^3J_{\text{H,H}} = 3.3$, 1.7 Hz, 1H, CH, *Z* isomer), 6.33 (dd, $^3J_{\text{H,H}} = 3.2$, 1.7 Hz, 1H, CH, *E* isomer), 6.25 (d, $^3J_{\text{H,H}} = 3.3$ Hz, 1H, CH, *Z* isomer), 6.19 (d, $^3J_{\text{H,H}} = 11.9$ Hz, 1H, CH, *Z* isomer), 6.12 (d, $^3J_{\text{H,H}} = 3.2$ Hz, 1H, CH, *E* isomer), 5.56 (dt, $^3J_{\text{H,H}} = 11.8$, 7.3 Hz, 1H, CH, *Z* isomer), 2.44 (ddt, $^3J_{\text{H,H}} = 7.4$, 7.4 Hz, $^4J_{\text{H,H}} = 1.6$ Hz, 2H, CH_2 , *Z* isomer), 2.17 (dt, $^3J_{\text{H,H}} = 7.0$, 7.0 Hz, 2H, CH_2 , *E* isomer), 1.48 (quin, $^3J_{\text{H,H}} = 7.4$ Hz, 2H, CH_2 , *Z* isomer), 1.45 (quin, $^3J_{\text{H,H}} = 7.4$ Hz, 2H, CH_2 , *E* isomer), 1.38–1.24 (m, 16H, $8 \times \text{CH}_2$, *E + Z* isomer), 0.89 (t, $^3J_{\text{H,H}} = 7.0$ Hz, 6H, $2 \times \text{CH}_3$) ppm. ^{13}C NMR (175 MHz, CDCl_3): $\delta = 153.6$ (C_q , *E* isomer), 153.6 (C_q , *Z* isomer), 141.3 (CH, *E* isomer), 141.3 (CH, *Z* isomer), 131.7 (CH, *Z* isomer), 130.5 (CH, *E* isomer), 118.6 (CH, *E* isomer), 117.3 (CH, *Z* isomer), 111.2 (CH, *E* isomer), 111.2 (CH, *Z* isomer), 108.8 (CH, *Z* isomer), 106.0 (CH, *E* isomer), 33.0 (CH_2 , *E* isomer), 32.0 ($2 \times \text{CH}_2$, *E + Z* isomer), 29.7 (CH_2 , *Z* isomer), 29.5 (CH_2 , *Z* isomer), 29.4 ($2 \times \text{CH}_2$, *E + Z* isomer), 29.4 (CH_2 , *E* isomer), 29.4 (CH_2 , *Z* isomer), 29.3 (CH_2 , *E* isomer), 29.3 (CH_2 , *E* isomer), 22.8 (CH_2 , *Z* isomer), 14.3 ($2 \times \text{CH}_3$, *E + Z* isomer) ppm. HR-APCI-MS: calcd. for $\text{C}_{13}\text{H}_{21}\text{O}^+$ 193.1587; found 193.1587. IR (ATR): $\nu/\text{cm} = 3026$ (w), 2956 (m), 2925 (s), 2855 (s), 1735 (w), 1583 (w), 1492 (w), 1459 (w), 1256 (w), 1218 (w), 1175 (w), 1150 (w), 1058 (w), 1013 (m), 960 (w), 923 (w), 885 (w), 804 (w), 729 (s), 595 (w) cm^{-1} . UV-vis (CH_2Cl_2): λ_{max} ($\log \epsilon$) = 274 (3.61), 263 (3.83) nm.

2-(Undec-1-en-1-yl)furan (46). Prepared from decyltriphenylphosphonium iodide (**44**, 2.65 g, 5.00 mmol). Yield: 881 mg (4.00 mmol, 80%, *Z/E* 3:1). TLC (cyclohexane): $R_f = 0.85$. ^1H NMR (700 MHz, CDCl_3): $\delta = 7.34$ (d, $^3J_{\text{H,H}} = 1.7$ Hz, 1H, CH, *Z* isomer), 7.30 (d, $^3J_{\text{H,H}} = 1.5$ Hz, 1H, CH, *E* isomer), 6.39 (dd, $^3J_{\text{H,H}} = 3.3$, 1.8 Hz, 1H, CH, *Z* isomer), 6.34 (dd, $^3J_{\text{H,H}} = 3.3$, 1.8 Hz, 1H, CH, *E* isomer), 6.25 (d, $^3J_{\text{H,H}} = 3.3$ Hz, 1H, CH, *Z* isomer), 6.18 (d, $^3J_{\text{H,H}} = 11.8$ Hz, 1H, CH, *Z* isomer), 6.12 (d, $^3J_{\text{H,H}} = 3.3$ Hz, 1H, CH, *E* isomer), 5.56 (dt, $^3J_{\text{H,H}} = 11.7$, 7.3 Hz, 1H, CH, *Z* isomer), 2.43 (ddt, $^3J_{\text{H,H}} = 7.3$, 7.3 Hz, $^4J_{\text{H,H}} = 1.6$ Hz, 2H, CH_2 , *Z* isomer), 2.17 (dt, $^3J_{\text{H,H}} = 7.1$, 7.1 Hz, 2H, CH_2 , *E* isomer), 1.47 (q, $^3J_{\text{H,H}} = 7.3$ Hz, 2H, CH_2 , *Z* isomer), 1.45 (q, $^3J_{\text{H,H}} = 7.5$ Hz, 2H, CH_2 , *E* isomer), 1.39–1.22 (m, 24H, $12 \times \text{CH}_2$, *E + Z* isomer), 0.89 (t, $^3J_{\text{H,H}} = 7.2$ Hz, 6H, $2 \times \text{CH}_3$, *E + Z* isomer) ppm. ^{13}C NMR (175 MHz, CDCl_3): $\delta = 153.6$ (C_q , *E* isomer), 153.6 (C_q , *Z* isomer), 141.3 (CH, *E* isomer), 141.3 (CH, *Z* isomer), 131.7 (CH, *Z* isomer), 130.5 (CH, *E* isomer), 118.6 (CH, *E* isomer), 117.3 (CH, *Z* iso-

mer), 111.2 (CH, *E* isomer), 111.2 (CH, *Z* isomer), 108.8 (CH, *Z* isomer), 106.0 (CH, *E* isomer), 33.0 (CH_2 , *E* isomer), 32.0 ($2 \times \text{CH}_2$, *E + Z* isomer), 29.7 (CH_2 , *Z* isomer), 29.7 (CH_2 , *E* isomer), 29.7 (CH_2 , *Z* isomer), 29.7 ($2 \times \text{CH}_2$, *E + Z* isomer), 29.6 (CH_2 , *Z* isomer), 29.5 ($2 \times \text{CH}_2$, *E + Z* isomer), 29.4 (CH_2 , *Z* isomer), 29.4 (CH_2 , *E* isomer), 29.4 (CH_2 , *E* isomer), 22.8 (CH_2 , *Z* isomer), 14.3 ($2 \times \text{CH}_3$, *E + Z* isomer) ppm. HR-APCI-MS: calcd. for $\text{C}_{15}\text{H}_{25}\text{O}^+$ 221.1900; found 221.1897. IR (ATR): $\nu/\text{cm} = 2956$ (m), 2925 (s), 2854 (s), 1492 (w), 1465 (w), 1150 (w), 1120 (w), 1086 (w), 1039 (w), 1013 (w), 959 (w), 936 (w), 922 (w), 884 (w), 800 (w), 723 (s), 654 (w), 622 (w), 595 (w) cm^{-1} . UV-vis (CH_2Cl_2): λ_{max} ($\log \epsilon$) = 274 (3.76), 263 (3.93) nm.

Conflicts of interest

There are no conflicts to declare.

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