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Substituted Hepta-1,6-dien-3-ones with Green/Fruity Odours Green/Galbanum Olfactophore Model

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Abstract—Following an analysis of available SAR data on green/galbanum-smelling molecules, a series of new 2-substituted hepta-1,6-dien-3-ones and their analogues were prepared and their olfactory properties evaluated. The study allowed to select efficient new odourants—potential substitutes for natural galbanum oil—and to generate an *olfactophore* model for the green/galbanum note.

Introduction

QSAR studies in the domain of olfaction are difficult to carry out because of the elusive definition of 'activity', let alone its measurement.[1] Even within a given odour family, for example, *woody*, *musky* or *green*, the odour quality changes from one structure to another in an almost continuous spectrum of shades and nuances. In addition, it often varies with the concentration, that is, over time. This phenomenon is mainly due to the complexity of the olfactory mechanism, in the *primary event* of which molecules of a defined structure bind simultaneously to several of probably up to 1000 different receptor types. Unequal sensitivities of the activated receptors towards the same odourant may be responsible for more or less pronounced changes of its odor profile with the concentration. Moreover, a single receptor protein may interact with several different ligands.[2] In other words, each odour sensation is triggered by a chord played on a 'keyboard' of odourant receptors—in agreement with the recently proven combinatorial coding of odour perception[3]—and these chords are often partially superposable.

On the other hand, the high variability of the astonishingly big olfactory repertoire of the human genome[4] gives rise to frequent *hyper*- *hypo*- and *an-osmias* (abnormal sensitivities to a given odour). This hampers the acquisition of significant structure–odour relationship data not only in terms of the odour quality, but also of its static and dynamic quantity, that is, the perception threshold and duration.[5] Despite recent progress in the functional expression of odourant receptors[6] which belong to the omnipresent family of **G p**rotein **c**oupled **r**eceptors (GPCRs), no practical assay to measure odourant–olfactory receptor affinity is currently available.[7] At present, a rational odourant design is hardly possible and most often limited to the classical 'me-too' or 'mecano' approaches.[8]

All these difficulties notwithstanding, fragrance chemists keep searching for *olfactophores*, that is, common electronic shapes of the *active* conformers of different chemical structures responsible for the same (or very similar) odour sensations.[1b,c] These entities, analogous to the *pharmacophores* used in the medicinal chemistry, would allow applications of the well established methodologies of *lead* finding and optimisation. Because of the above-mentioned limitations, a routine QSAR approach to the *olfactophore* search is impossible at this point. However, for preliminary studies *training set* structures can be classified into two or three groups: active, inactive and those with an intermediate activity, that is, significantly weaker and/or of a less similar olfactory profile compared to the template molecule(s).

Galbanum oil and resinoid, produced from *Ferula galbaniflua* Boissier and Buhse and *Ferula rubricaulis* Boissier growing in Iran,[9] are important perfumery raw materials of a characteristic harsh, green, slightly spicy and fruity odour. They are complex mixtures of products in which minor constituents, particularly (3*E*,5*Z*)-

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undeca-1,3,5-triene[‡] (**1**; Fig. 1), play important olfactory roles. Since the serendipitous discovery of Dynascone® (**2**; main olfactory constituent), having a green/galbanum, fruity (pineapple-like) scent,[13] the galbanum-type odourants have been widely applied in fine and functional perfumery, most often to impart fruity-green notes.[1c] The odour of Dynascone® (**2**) resembles that of undecatriene **1**, but is significantly less fatty and more fruity. The fruity-pineapple aspect is even more present in other similar synthetic products such as **3**,[14] **4**[15] and **5**.[16,17]

Results and Discussion

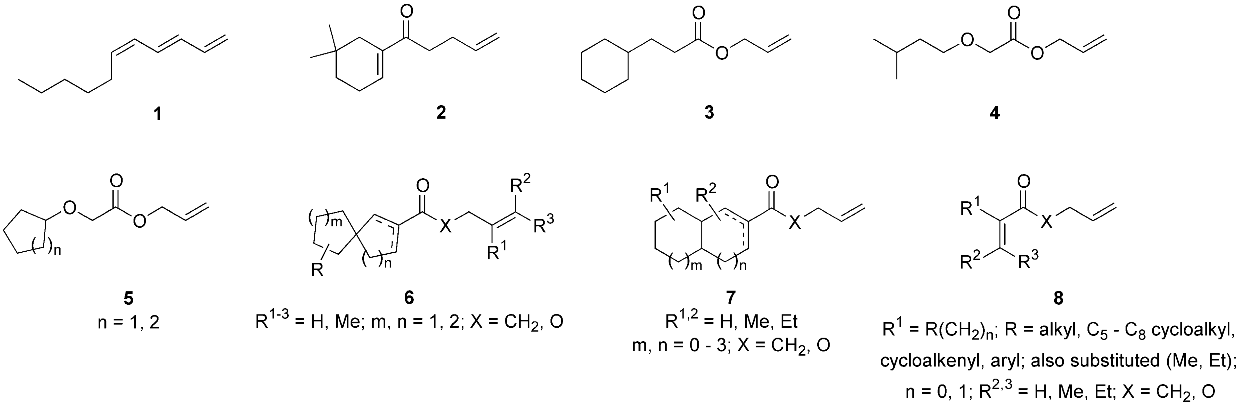
Chemistry and structure–odour relationships (SORs)

Looking for more efficient—that is, more intense and substantive (long-lasting) and less costly—substitutes of galbanum oil, we have recently prepared and claimed series of bicyclic derivatives **6**[18] and **7**.[19,20] The conjugated C=C bond appears to enhance significantly the green/galbanum odour note of these products. Its position in the ring is also important; it has already been found[13a] that the odour of α-Dynascone® (**2**) is much stronger than that of its β isomer (**34** in Table 2), the latter having no galbanum character. This tendency was confirmed for the spiro-analogues **6**.

In order to further probe the spatial requirements of the possible lipophilic pocket of a galbanum-type odourant receptor, and to find the best position of the conjugated C=C bond, a series of substituted hepta-1,6-dien-3-ones **8** was prepared according to the reaction in Scheme 1. Different 2-substituents (alkyls; cycloalk(en)yls, aryls, with and without a spacer), as well as other structural modifications, such as simple mono- and di-substitution of the conjugated methylene group (**8b**, **8s** and **8q**; Table 1) and its replacement by an isoelectronic and tentatively bioisosteric cyclopropane ring (**24a** and **24b**; Scheme 2), were tried. The olfactory importance of the *gem*-dimethyl group is well known among fragrance chemists, and rather astonishing examples where the 1,1-dimethylcyclohexyl moiety was replaced by the eight-membered ring without significant change of the scent (especially within the amber/woody note) of such modified odourants were reported.[21] Therefore, we also prepared isomeric *tert*-butylcyclohexyl and cyclooctenyl analogues of **2** (**28a–d**), according to the usual reaction sequence depicted in Scheme 3.

The already mentioned series of bicyclic structures **7** ($X = CH_2$), mimicking **2** and **6**, was obtained[19] in the same way. These complex mixtures of stereoisomers were of little help for this study. Nevertheless, the main odour vector of 1-(octahydronaphthalen-2-yl)pent-4-en-1-one **7a**, one of the best compounds of the series, was isolated by preparative GC, its structure was elucidated and its odour measured and evaluated. The olfactory properties of the corresponding intermediate alcohols and the 1,2- and 6,7-dihydro- (Scheme 2) and 4-oxa[20] analogues of the best rated candidates were compared to those of the parent hepta-1,6-dien-3-ones to confirm the contribution of the carbonyl group (ketone versus ester) and both C=C double bonds to the total odour sensation and to generate a possibly reliable green/galbanum *olfactophore* model.

The syntheses of compounds **8** are straightforward and easy to apply on an industrial scale.[22] The most general one (Scheme 1) consists of a Mannich methylenation of an aldehyde, followed by addition of the Grignard reagent prepared from 4-bromobut-1-ene (commercially available and easily accessible from 1,4-dibromobutane) and a smooth oxidation of the resulting allylic alcohols **15**. The α,β-unsaturated aldehydes, necessary to prepare the ethylidene and propylidene homologues (**8b** and **8s**) of **8a**—one of the most promising candidate for development and introduction into the perfumers' palette—were obtained by cross-aldol condensation under the Mukaiyama conditions[23] followed by dehydration. The most strained isopropylidene analogue **8q** was synthesised via cyclohexylacetate anion addition to acetone. An alternative preparation of **8** consists of condensation of a ketone with ethyl cyanoacetate followed by reduction of the α,β-unsaturated ester group, TMS protection



1

2

3

4

5
n = 1, 2

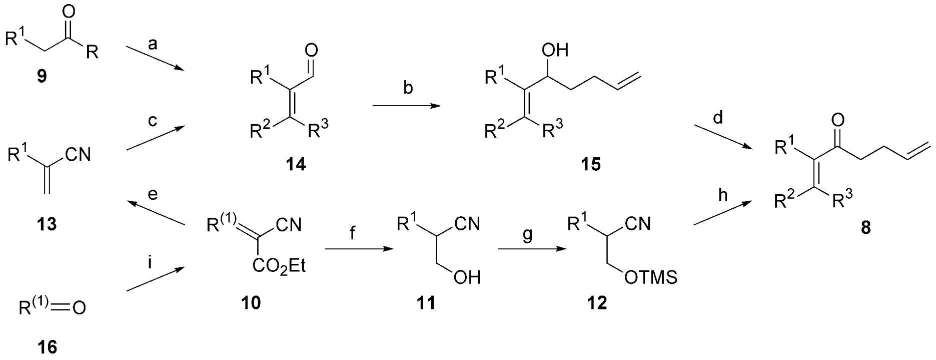
6
R^{1-3} = H, Me; m, n = 1, 2; X = CH_2, O

7
$R^{1,2}$ = H, Me, Et
m, n = 0 - 3; X = CH_2, O

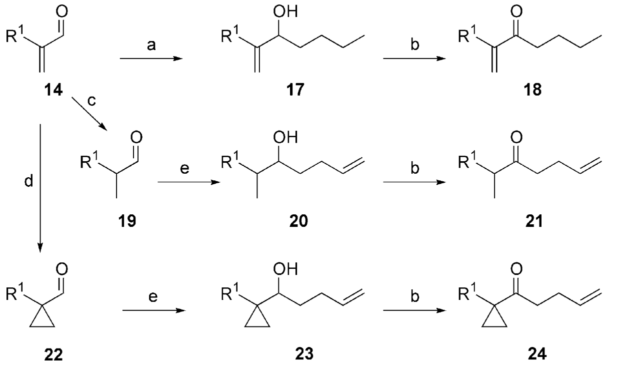
8
R^1 = $R(CH_2)_n$; R = alkyl, C_5 - C_8 cycloalkyl, cycloalkenyl, aryl; also substituted (Me, Et);
n = 0, 1; $R^{2,3}$ = H, Me, Et; X = CH_2, O

Figure 1. Important green/galbanum smelling compounds.

[‡] **1**, often called 'galbanolene' because of its origin and odour,[10] is widespread in nature. It has been found in fruits and vegetables[11] and constitutes a powerful pheromone of marine brown algae; as a sperm attractant in *Cystophora siliquosa* J. Ag., it was given the name of 'cystophorene'.[12]



Scheme 1. Preparation of hepta-1,6-dien-3-ones **8**: (a) R, R^2, R^3 = H: CH_2O, Et_2NH, H_2SO_4; R, R^2 = H, R^3 = Me, Et: (1) TMSCl, Et_3N, DMF; (2) R^2CHO, $TiCl_4$, $Ti(O^iPr)_4$; (3) I_2, Δ; R = OEt, R^1, R^2 = Me: (1) LDA, AcMe; (2) LAH; (3) MnO_2; (b) $CH_2{=}CH(CH_2)_2MgBr$; (c) DIBAH; (d) MnO_2 or PCC/CH_2Cl_2; (e) (1) H_2, Pd/C; (2) KOH; (3) HCl; (4) CH_2O, pyridine; (f) $NaBH_4$; or (1) H_2, Pd/C; (2) $NaBH_4$; (g) TMSCl, NEt_3; (h) (1) $CH_2{=}CH(CH_2)_2MgBr$, toluene; (2) H^+; (i) $NCCH_2CO_2Et$, $AcNH_4$, AcOH.



Scheme 2. Preparation of analogues of **8**: (a) *n*-BuMgBr; (b) MnO_2 or PCC/CH_2Cl_2; (c) H_2, Pd/C; (d); $Me_2S(O){=}CH_2$; (e) $CH_2{=}CH(CH_2)_2$-MgBr, toluene.

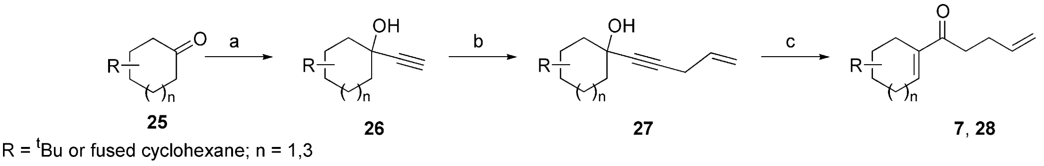
of the obtained cyanoalcohol and a one pot Grignard addition/dehydration step. A cyclopropane ring was introduced via the Corey–Chaykovsky reaction (**24a** and **24b**), while hydrogenation of the intermediate α,β-unsaturated aldehyde **14** and the use of a saturated Grignard reagent provided the corresponding hepten-3-ones **21** and **18** (Scheme 2). The syntheses of 1-(*tert*-butylcyclohexyl), 1-cyclooctenyl and 1-octalinylpent-4-en-1-ones **28a–d** and **7a** via the Meyer–Schuster rearrangement of the corresponding propargylic alcohols **27** were analogous to the published experimental procedures for similar structures[13b,18,19] (Scheme 3).

The results of olfactory evaluations (predominance of the green/galbanum odour character and intensity of this odour note) and odour thresholds (the lowest concentration at which any odour of the material is perceived) measured by the GC sniffing methods[24] are shown in Table 1. The ketones are sorted by increasing GC OT, their green/galbanum odour note intensity[§] is indicated by three descriptors: *high*, *medium*, and *low*. For the sake of clarity, only two simple (no diastereoisomerism) alcohols **15** corresponding to the most active ketones are included, as their scents were always weaker and very different from the green/galbanum one.

These structure-odour relationship (SOR) data confirm the importance of the three electron rich structural features: a carbonyl group and both C=C double bonds. Astonishingly, and contrary to our previous results in the domain of sandalwood odourants,[28,29] the replacement of the Δ^1 C=C double bond by a cyclopropane ring resulted in a total loss of the green galbanum scent (**8a**≫**24b**). It became also clear that slight differences in the steric hindrance of the bulky group can lead to dramatic changes in the olfactory properties of apparently very similar structures: for example, **8d**≫**8l** (*trans* vs *cis*); **8c**>**8m** (*cis* vs *trans*); **8a**>**8e**=**8f**>**8o** and **8c**>**8i** (ring size difference); **8a** >**8k** (cyclohexyl linked directly or via a CH_2 spacer); **8a**=**8b** >**8q**=**8s** (small substituents at C_1).

Olfactophore model

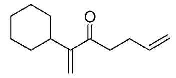
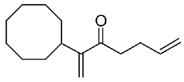
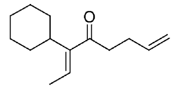
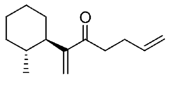
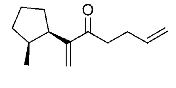
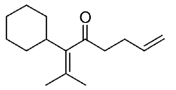
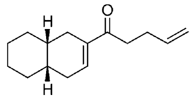
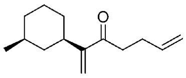
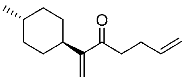
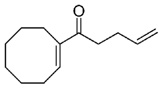
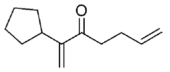
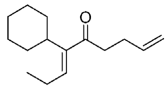
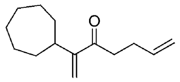
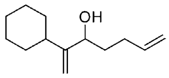
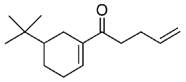
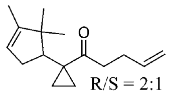
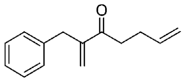
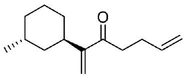
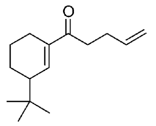
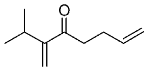
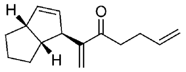
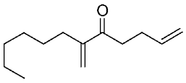
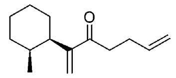
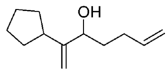
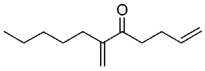
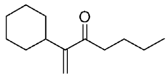
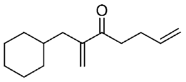
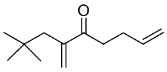
In the generation of the green/galbanum *olfactophore* model only single stereoisomer and racemic molecules were selected among active and intermediate compounds. Up to four stereoisomer mixtures were allowed in the third group of inactive ones (Table 1). The Catalyst™ software[30] we used for the *olfactophore* generation is well suited for such cases of undefined absolute configuration.[31] Also, our GC-sniffing technique of odour analysis makes low the risk of false negatives due to a possible antagonistic effect of a constituent.



Scheme 3. Preparation of substituted cycloalkenylpent-4-en-1-ones **7** and **28**: (a) C_2H_2, ᵗBuOK; (b) KOH, $H_2C{=}CHCH_2Cl$, CuCl; (c) HCO_2H, Δ.

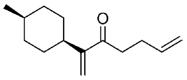
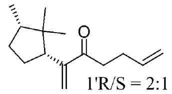
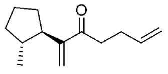
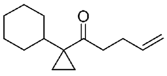
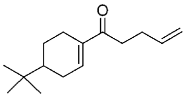
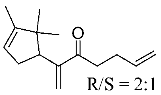
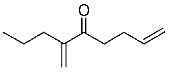
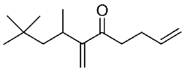
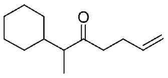
[§] In other words, the strength of the green/galbanum component of the overall odour.

Table 1. Substituted hepta-1,6-dien-3-ones and their analogues, prepared and used in the green/galbanum *olfactophore* generation; sorted by increasing odour threshold order

Compd	Structure[a]	GC OT[b]	Green/ galbanum odour intensity[c]	Conf.[d]	Fit[e]	Δ *E*[f]	Compd	Structure[a]	GC OT[b]	Green/ galbanum odour intensity[c]	Conf.[d]	Fit[e]	Δ *E*[f]
8a		1	High	221	10.8	5.1	**8o**		10^{2}	Medium	51	10.3	6.2
8b		1	High	190	10.2	5.4	**8p**		$2\cdot10^{2}$	Medium *metallic, green*	28	8.9	3.5
8c		2	High	40	10.0	8.6	**8q**		$2\cdot10^{2}$	Medium *fruity, sweet*	201	9.0	9.8
7a		2	High	44	11.0	0.0	**8r**		$2\cdot10^{2}$	Medium *green, fruity*	54	10.5	9.5
8d		4	High	38	10.2	9.4	**28d**		$2\cdot10^{2}$	Medium *fruity, pear*	24	8.1	8.7
8e		9	High	192	10.0	5.9	**8s**		$2\cdot10^{2}$	Medium *green, fruity*	34	9.7	0.0
8f		10	High	237	10.0	3.6	**15a**		$3\cdot10^{2}$	Low *fruity, green*	440	8.8	2.4
28a		10	High	41	10.6	7.6	**24a**		$3\cdot10^{2}$	Low *animal, green*	77	9.4	0.0
8g		20	Low *rosy, fruity*	44	9.5	8.4	**8t**		$4\cdot10^{2}$	Medium *green, fruity*	49	9.5	8.9
28b		30	Low *green, fatty*	32	9.2	8.8	**8u**		$4\cdot10^{2}$	Low *green, plastic*	32	8.1	4.2
8h		40	High	212	10.6	1.8	**8v**		$4\cdot10^{2}$	Low *metallic, tarragon*	86	10.6	6.7
8i		60	High	26	9.1	9.4	**15e**		$5\cdot10^{2}$	Low *metallic*	425	8.5	7.5
8j		60	Medium *apple, pineapple*	62	10.7	4.0	**18**		$8\cdot10^{2}$	Low *acidic, fruity*	24	9.2	4.6
8k		90	Medium	41	9.9	8.5	**8w**		$9\cdot10^{2}$	Low *anisic*	17	8.5	5.2

(*continued on next page*)

Table 1 (*continued*)

Compd	Structure[a]	GC OT[b]	Green/ galbanum odour intensity[c]	Conf.[d]	Fit[e]	Δ E[f]	Compd	Structure[a]	GC OT[b]	Green/ galbanum odour intensity[c]	Conf.[d]	Fit[e]	Δ E[f]
8l		10^2	Low *dill*	57	9.2	5.6	**8x**		10^3	Low *woody, amber*	145	9.2	2.8
8m		10^2	Medium *green*	37	10.4	4.1	**24b**		$2\cdot10^3$	Low *green, pineapple*	218	8.0	9.3
28c		10^2	Low *fruity, liquor*	82	8.3	6.6	**8y**		$4\cdot10^3$	Low *sandalwood*	7.7	10.0	9.2
8n		10^2	Low *green, fruity*	48	10.7	2.7	**8z**		$5\cdot10^3$	Low *waxy, fruity*	88	9.4	3.5
21		10^2	Low *fruity, pineapple*	458	8.4	8.6							

[a] Relative configuration, racemate(s) if not otherwise stated.

[b] Measured using the GC/sniff technique[24] on a *DB*™*-1* or *DB*™*-5* 15 m × 0.53 mm/1.5 μm column by 3–5 panelists; relative values (per weight) compared to **8a**.

[c] Evaluated by the GC/sniff technique[24] as in b, and on the blotter. In *italics* the main odour note if not predominantly green/galbanum; only the main two odour descriptors are reported.

[d] Number of conformers ('best' mode) for the *olfactophore* generation.

[e] Quality of the compound mapping to the *hypothesis* ('fast' mode). The fit value depends on the weights assigned to the *hypothesis* features and the displacements of the features from the centres of the location constraints; a perfect mapping would correspond to the fit value equivalent to the sum of the weights of the features (in our case 16.17; the weights of the features A, B_1, B_2, C and C′, depicted in Figure 2, being 2.89, 2.02, 2.02, 4.62, and 4.62, respectively).

[f] Strain energy difference between the best fitting and the most stable conformer (in kcal/mol).

A training set of 37 compounds described in this paper (10 active, 10 medium and 17 inactive; Table 1) was completed by 25 similar molecules reported elsewhere (Table 2). The undecatriene **1**, structurally very different and difficult to classify because of the strong (and in our view detrimental) fatty note that accompanies its very intense green odour, was not included.

The methodology applied to the generation of the green/galbanum *olfactophore* model was similar to those reported for other odour notes.[1b,1c,28,29] In the first step, the *conformational model*[‖] that covers the whole conformational space was built for each of the 74 structures of the training set; the stereoisomers of inactive compounds were considered as separate structures. Applying a 10 kcal/mol energy cutoff,[32] between 25 and 237 conformations were obtained for each structure, depending on its conformational flexibility (Tables 1 and 2). In order to derive quantitative *olfactophore* models (HypoGen[33]), the three categories of structures—endowed with *high*, *medium* and *low* green/galbanum odour intensity—were arbitrarily assigned a biological *activity* of 10^{-5}, 10^{-3} and 0.1, respectively. The gener-

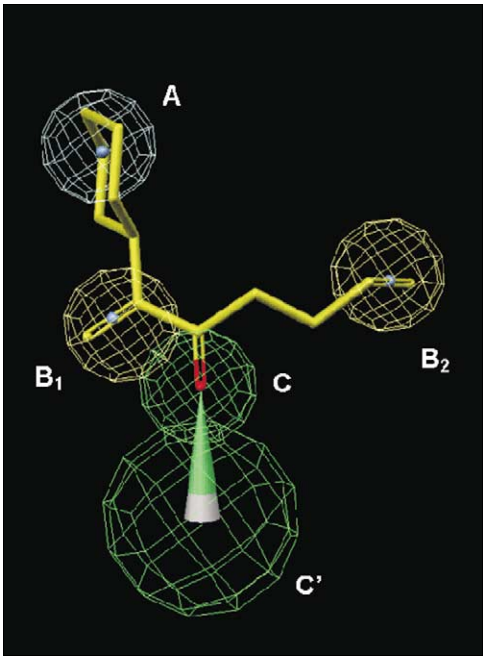
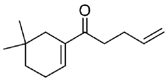
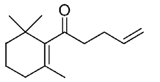
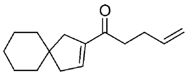
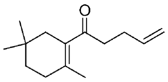
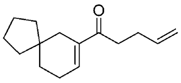
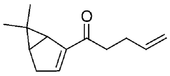
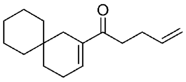
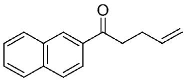
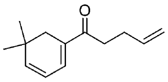
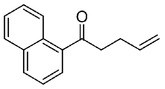
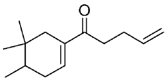
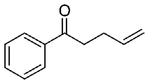
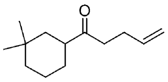
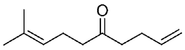
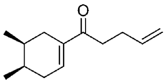
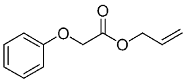
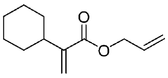
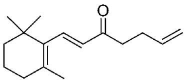
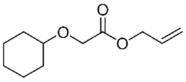
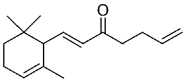
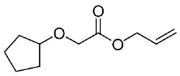
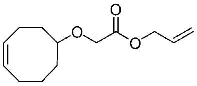
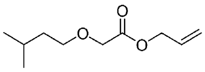
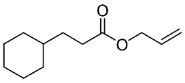
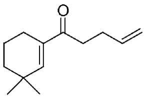


Figure 2. **8a** mapping the green/galbanum *olfactophore* model. **A**: hydrophobe, **B**^{n}: C=C or ether, **C**→**C**′: HBA.

[‖] For exact definitions of the Catalyst™ terms (in *italics* when first cited in the text) and methodology see (ref 31).

Table 2. Other training set structures used in the *olfactophore* generation

Compd	Structure[a]	Lit.[b]	Green/ galbanum odour intensity[c]	Conf.[d]	Fit[e]	ΔE[f]	Compd	Structure[a]	Lit.	Green/ galbanum odour intensity[c]	Conf.[d]	Fit[e]	ΔE[f]
2		13a	High	26	10.0	0.0	**35**		13a	Low *floral, green, fruity*	25	8.0	0.0
6a		18	High	25	11.0	4.7	**36**		13a	Low *floral (ionone-like)*	32	10.7	7.3
6b		18	High	43	10.7	0.0	**37**		13a	Low *fruity (mouldy)*	37	9.2	0.0
6c		18	High	32	9.3	6.7	**38**		25	Low *mushroom-earthy, floral*	44	8.3	0.1
29		13a	High	31	10.2	0.0	**39**		25	Low *amber-like, cistus*	74	8.7	3.4
30		13a	Medium *floral (ionone-like)*	41	9.8	7.5	**40**		25	Low *floral, green, aromatic*	19	7.4	0.2
31		13a	Medium	26	8.6	2.6	**41**		25	Low *pineapple*	44	9.0	2.3
32		13a	Medium *fruity*	57	10.6	3.6	**42**		13a 26	Low *fruity (pineapple)*	57	9.1	3.6
8A		20	Medium *fruity, pineapple*	228	10.5	1.2	**43**		13a 25	Low *floral (ionone), woody, marine*	51	9.9	7.7
5a		13a 17	Medium *fruity (pineapple)*	34	9.6	4.5	**44**		13a 25	Low *floral, fruity, woody*	84	9.3	1.4
5b		16	Medium *rose, green apple*	32	8.7	4.4	**45**		27	Low *pineapple, camomile*	198	2.9	9.7
4		13a 15	Medium	64	9.6	8.1	**3**		14	Low *sweet-fruity (pineapple)*	49	8.0	2.3
34		13a	Low *floral, fruity*	43	8.6	1.8							

[a] Racemates for chiral structures.
[b] Source of odour descriptions.
[c] In *italics* the main odour note if not predominantly green/galbanum.
[d] Cf. Table 1.
[e] Cf. Table 1.
[f] Cf. Table 1.

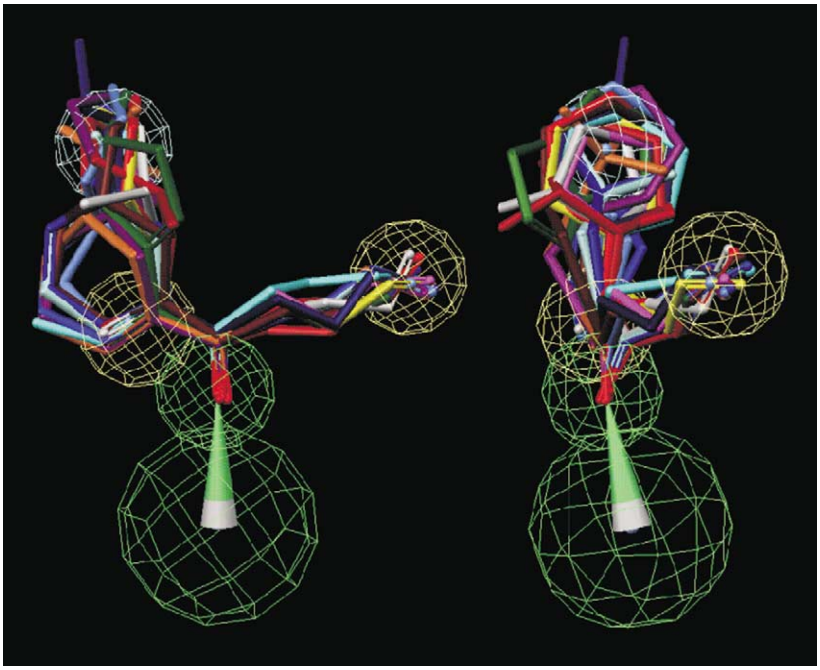


Figure 3. All the 15 best green/galbanum odorants from the training set aligned on the *olfactophore* model; front (left) and side view.

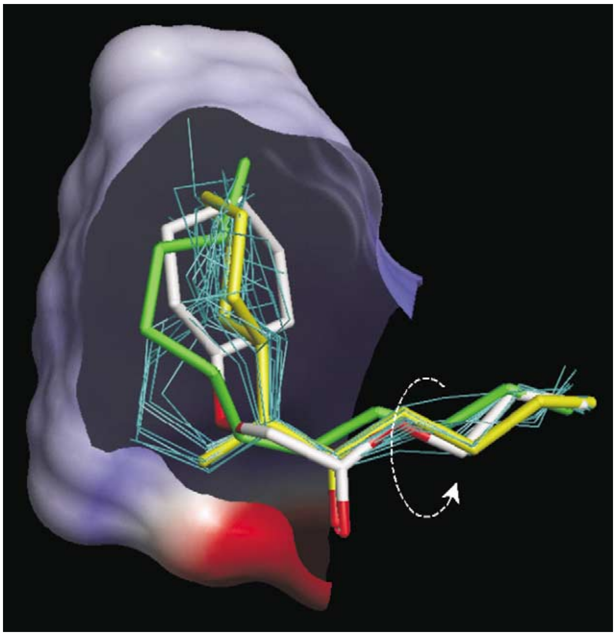


Figure 4. Connolly surface, generated on the alignment from Figure 3. **8a** and two structurally different strong green/galbanum odorants **1** (green) and **5a** (white), also aligned on the model but not used in the surface generation, are highlighted.

ated models (also called *hypotheses*) are 3D arrangements of selected chemical features, that best correlate with the input activity data. In our case, they were composed of an oriented *hydrogen-bond acceptor* (HBA), 2–4 *hydrophobes* and 1–2 custom *functions*, the latter corresponding either to a C=C double bond or to an C–O–C ether group.

Independent variation of the interpharmacophore feature *spacing*, *weight* and *tolerance* factors and of the minimum and maximum number and type of functions led to a series of hypotheses with a satisfactory predictive character. They all consist of a set of one *hydrophobe* and one custom double bond/ether function that represents the bulky lipophilic part of a green/galbanum odourant, and of another double bond/ether function and an HBA, corresponding to the side-chain bearing the *osmophoric*[1b] carbonyl group. This series of similar hypotheses differs by the positions of the two functions mapped by the side chain, due to the flexibility of the pent-4-enoyl and allyloxycarbonyl fragments of the training set structures.

The best hypothesis (*correlation*[34] 0.6), mapped by the best green/galbanum odourant from this study (**8a**) and by all the strong odourants with this odour from the training set, is depicted in Figures 2 and 3, respectively.

While it was impossible to unequivocally determine the best relative positions of the HBA and of the side-chain hydrophobe, the bulky lipophilic part of the *olfactophore* could be fairly well defined. The Connolly surface[35] of these parts of the best 15 molecules aligned on the best hypothesis (Fig. 4) could represent the lipophilic pocket of the green/galbanum receptor(s). For the inactive molecules, structurally closely related to the active ones, which map all the functions of our best hypotheses (cf. *fit* parameter in Tables 1 and 2) this surface constitutes a good discrimination tool.[36]

The undecatriene **1**, of a much more fatty and less fruity odor than those of the active compounds from this study, maps very well all the functions of the best hypothesis except the HBA (Fig. 3).

Conclusions

This study allowed to prepare new, excellent green/galbanum-type odourants and to increase the pool of analogues indispensable to acquire useful structure–odour relationship (SOR) data. Their analysis gave rise to an *olfactophore* model for this type of odour, which—whatever its limitations—has already proved useful in the design of new odourants. Further research is necessary to define the exact geometry of the flexible part of active structures. However, our preliminary results indicate that any side-chain substitution decreases the green/galbanum odour intensity.

It should be kept in mind that, because of the proved combinatorial coding of odour perception,[3] the complete model of an *olfactophore* consists probably of several hypotheses (electronic shapes), corresponding to a set of different receptors, the activation of which is prerequisite to the odour sensation. Consequently, some flexibility of the butenyl side chain could be indispensable for odourants to adapt to the binding sites of all the receptors of the green/galbanum accord. In this respect, the less well-correlated Catalyst™ hypotheses could also be useful.

Experimental

General

All reagents and solvents were commercially available and were used without any purification. All products reported were obtained as colourless oils, if not otherwise stated.

GC: *DB™-WAX*, *DB™-1*, *DB™-5*, and *DB™-1701* columns. Flash chromatography: Merck silica gel 60 (230–400 mesh). TLC: Merck silica gel 60 F_{254} anal. plates. IR spectra: Bruker Vector 22 with Harrick ATR SplitPea™ device; neat (ATR); in cm^{-1}. NMR: Bruker DPX-400; ^1H at 400 and ^{13}C at 100 MHz; in $CDCl_3$; chemical shifts (δ) in ppm downfield from TMS; coupling constants J in Hz; NOESY, and GRASP COSY-DQF, HMBC and HMQC data were used in signal attributions. MS and GC/MS: Finnigan MAT 212 and Hewlett Packard MSD 5973 (EI, 70 eV) with HP-5MS column; intensities (in brackets) in % rel. to the base peak. HRMS: Finnigan MAT 95 (EI, 70 eV). Elemental analyses (C, H): Carlo Erba EA 1108; the results are within 0.4% of theoretical values. Molecular modelling: on SGI Octane R12000 workstation using Catalyst™ (generation of *conformational models* and *olfactophore hypotheses*)[30] and Moloc[35] (surfaces) software. Conformational model generation ('best' mode, $\Delta E = 10$ kcal/mol) were repeated till no new conformers were added. The best hypothesis was generated with spacing = 100 pm, and variable weight and tolerance.

General procedure for the synthesis of hepta-1,6-dien-3-ones 8

Method A; via acroleins 14. 2-Cyclohexylpropenal (14a). Successively, sulphuric acid 62% (79 g, 0.5 mol), aqueous formaldehyde 35% (82 g, 1.0 mol) and cyclohexylacetaldehyde (101 g, 0.8 mol) were added slowly to diethylamine (73 g, 1.0 mol) at 0 °C. After stirring at 80 °C overnight, the reaction mixture was extracted with MTBE. The combined organic phases were washed with H_2O until neutral pH, dried ($MgSO_4$) and concentrated in vacuo. The crude product was distilled under reduced pressure using a Widmer column (80 °C/10 torr) to give **14a**[37] (89.5 g, 81%). ^1H NMR: δ 9.51 (s, 1H), 6.21 (s, 1H), 5.94 (s, 1H), 2.47 (tt, $J = 11.9$, 2.9, 1H), 1.82–1.67 (m, 5H), 1.43–1.28 (m, 2H), 1.26–1.07 (m, 3H). ^{13}C NMR: δ 194.7 (d), 155.5 (s), 132.7 (t), 35.8 (d), 32.0 (2t), 26.4 (2t), 26.1 (t). MS: 138 (M^+, 40), 123(22), 109(73), 95(90), 91(28), 79(61), 67(100), 55(39), 41(53). IR: ν_{max} 2927vs, 2853s, 2701w, 1694vs, 1624w, 1449m, 1265m, 943m, 892m.

2-Cyclohexylhepta-1,6-dien-3-ol (15a). A solution of **14a** (69 g, 0.5 mol) in Et_2O (100 mL) was slowly added to but-1-enylmagnesium bromide prepared by addition of 4-bromobut-1-ene (81 g, 0.6 mol) in 100 mL of ether to magnesium turnings (13.2 g, 0.55 mol) in 300 mL of ether at 0 °C. The reaction mixture was then allowed to warm to room temperature and was stirred for additional 3 h and quenched with 2 N HCl. The organic layer was washed with H_2O until neutral pH, dried ($MgSO_4$) and concentrated in vacuo. The crude product was distilled using a Vigreux column (91 °C/0.15 torr) to give **15a** (85 g, 88%). ^1H NMR: δ 5.85 (ddt, $J = 17.1$, 10.2, 6.6, 1H), 5.05 (dq, $J = 17.1$, 1.8, 1H), 5.04 (t, $J = 1.0$, 1H), 4.98 (ddt, $J = 10.2$, 2.0, 1.1, 1H), 4.88 (s, 1H), 4.09 (dd, $J = 7.8$, 5.3, 1H), 2.25–2.06 (m, 2H), 1.89 (tt, $J = 11.4$, 2.7, 1H), 1.80–1.55 (m, 8H), 1.35–1.05 (m, 5H). ^{13}C NMR: δ 158.0 (s), 138.3 (d), 114.6 (t), 107.7 (t), 74.1 (d), 40.4 (d), 35.0 (t), 33.9 (t), 33.3 (t), 30.0 (t), 26.8 (t), 26.7 (t), 26.1 (t). MS: 194 (M^+, 1), 176(4), 165(3), 151(9), 139(11), 122(11), 109(15), 95(37), 83(66), 79(43), 71(34), 67(50), 55(100), 41(50). IR: ν_{max} 3361s, 3076w, 2926vs, 2852s, 1641w, 1448m, 1064m, 907s, 889m. Anal. calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.50; H, 11.43%.

2-Cyclohexylhepta-1,6-dien-3-one (8a). **15a** (85 g, 0.44 mol) was oxidised with MnO_2 (804 g, 9.2 mol) in hexane (2 L) at room temperature. After stirring for 96 h, the reaction mixture was filtered over Celite® and the solvent was evaporated in vacuo. Distillation (70 °C/0.04 torr) of the crude product (71 g) yielded **8a** (43.5 g, 51%). ^1H NMR: δ 5.95 (s, 1H), 5.83 (ddt, $J = 17.1$, 10.4, 6.5, 1H), 5.65 (d, $J = 1.1$, 1H), 5.04 (dq, $J = 17.1$, 1.7, 1H), 4.97 (ddt, $J = 10.4$, 1.7, 1.3, 1H), 2.77 (m, 2H), 2.57 (ttd, 11.9, 3.1, 1.0, 1H), 2.36 (dtt, 8.0, 6.5, 1.5, 2H), 1.80–1.65 (m, 5H), 1.41–1.28 (m, 2H), 1.24–1.01 (m, 3H). ^{13}C NMR: δ 201.3 (s), 154.3 (s), 137.3 (d), 121.2 (t), 115.0 (t), 37.5 (d), 37.2 (t), 32.6 (2t), 28.4 (t), 26.5 (2t), 26.2 (t). MS: 192 (M^+, 11), 177(4), 163(50), 149(29), 137(78), 121(9), 109(65), 95(22), 81(34), 77(12), 67(100), 55(61), 41(29). IR: ν_{max} 2926vs, 2852s, 1681vs, 1641w, 1449m, 1414w, 997w, 913m. Anal. calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.15; H, 10.48%.

The following **hepta-1,6-dien-3-ones 8** were prepared according to the general procedure A. Most of the acroleins **14** were obtained by the Mannich methylenation described for **14a**. The acroleins **14c + m**, **14i + p**, and **14o** were prepared via acrylonitriles 13. Their syntheses, as well as those of 3-monosubstituted acroleins **14b** and **14s**, intermediates in the preparation of **8b** and **8s**, are exemplified below. The unstable **14q**, difficult to purify, was prepared and used as a crude mixture with the intermediate 2-cyclohexyl-3-hydroxy-3-methylbutanal (vide infra).

(*E*)-3-Cyclohexylocta-2,7-dien-4-one (8b). Contained 10% of the (*Z*)-isomer. ^{1}H NMR: δ 6.49 (q, J = 7.1, 1H), 5.82 (ddt, J = 17.1, 10.3, 6.5, 1H), 5.02 (dq, J = 17.1, 1.7, 1H), 4.96 (ddt, J = 10.3, 1.8, 1.2, 1H), 2.68 (m, 2H), 2.54 (tt, J = 12.0, 3.4, 1H), 2.32 (dtt, J = 7.8, 6.5, 1.3, 2H), 1.87 (d, J = 7.1, 3H), 1.84–1.61 (m, 5H), 1.48–1.10 (m, 5H). ^{13}C NMR: δ 202.3 (s), 147.3 (s), 137.6 (d), 135.2 (d), 114.8 (t), 38.2 (d), 38.0 (t), 30.2 (2t), 28.7 (t), 27.1 (2t), 26.0 (t), 14.2 (q). MS: 206 (M^+, 10), 191(15), 177(16), 164(9), 151(100), 123(19), 109(8), 95(12), 81(80), 79(18), 67(43), 55(49), 41(20). IR: ν_{max} 2926vs, 2853s, 1672s, 1641w, 1450m, 1267w, 993w, 911m. HRMS: calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1672.

***cis*- and *trans*-2-(2-Methylcyclopentyl)hepta-1,6-dien-3-one (8c + 8m).** 14:9 mixture, separated on *DB*^{TM}*-5* column. **8c** (2nd eluted): ^{1}H NMR: δ 6.07 (s, 1H), 5.84 (ddt, J = 17.2, 10.5, 6.4, 1H), 5.66 (d, J = 1.5, 1H), 5.05 (dq, J = 17.2, 1.8, 1H), 4.98 (ddt, J = 10.2, 1.6, 1.3, 1H), 3.05 (m, 1H), 2.78 (m, 2H), 2.37 (m, 2H), 2.30 (m, 1H), 1.92 (m, 1H), 1.77–1.51 (m, 4H), 1.29 (m, 1H), 0.54 (d, J = 7.2, 3H). ^{13}C NMR: δ 201.6 (s), 150.0 (s), 137.4 (d), 122.8 (t), 115.0 (t), 43.6 (d), 37.1 (t), 34.6 (d), 33.4 (t), 28.5 (t), 27.7 (t), 22.7 (t), 16.8 (q). MS: 192 (M^+, 10), 177(14), 164(20), 163(56), 151(20), 149(27), 137(93), 135(15), 121(15), 110(22), 109(100), 107(22), 95(26), 81(52), 79(23), 67(96), 55(96), 53(31), 41(42), 39(27). HRMS: calcd for $C_{13}H_{20}O$: 192.1514. Found: 192.1525. **8m** (1st eluted): ^{1}H NMR: δ 6.00 (s, 1H), 5.84 (ddt, J = 17.2, 10.5, 6.9, 1H), 5.70 (d, J = 1.0, 1H), 5.04 (dq, J = 17.2, 1.6, 1H), 4.98 (ddt, J = 10.2, 1.6, 1.3, 1H), 2.82 (m, 2H), 2.49 (m, 1H), 2.37 (m, 2H), 2.02–1.84 (m, 3H), 1.63 (m, 2H), 1.36–1.19 (m, 2H), 0.91 (d, J = 6.3, 3H). ^{13}C NMR: δ 201.8 (s), 151.9 (s), 137.4 (d), 121.6 (t), 115.0 (t), 47.6 (d), 39.8 (d), 37.4 (t), 34.4 (t), 33.5 (t), 28.5 (t), 23.4 (t), 18.6 (q). MS: 192 (M^+, 12), 177(19), 164(32), 163(84), 151(23), 150(31), 149(27), 137(87), 135(19), 123(13), 121(17), 119(34), 110(23), 109(80), 107(25), 95(39), 93(27), 81(53), 79(29), 67(100), 55(96), 53(33), 43(31), 41(49). HRMS: calcd for $C_{13}H_{20}O$: 192.1514. Found: 192.1515. IR (**8c + 8m**): ν_{max} 2954vs, 2870s, 1681vs, 1641m, 1450m, 1413m, 1376m, 997m, 913s.

***trans*- and *cis*-2-(4-Methylcyclohexyl)hepta-1,6-dien-3-one (8d + 8l).** 25:22 mixture separated on *DB*^{TM}*-1* column. **8d** (2nd eluted): ^{1}H NMR: δ 5.96 (s, 1H), 5.83 (ddt, J = 17.1, 10.2, 6.5, 1H), 5.69 (d, J = 1.3, 1H), 5.03 (dq, J = 17.1, 1.6, 1H), 4.97 (ddt, J = 10.2, 1.7, 1.3, 1H), 2.77 (m, 2H), 2.52 (ttd, J = 11.6, 3.0, 1.0, 1H), 2.36 (m, 2H), 1.72–1.55 (m, 4H), 1.49–1.27 (m, 3H), 1.17–0.99 (m, 2H), 0.89 (d, J = 6.6, 3H). ^{13}C NMR: δ 201.4 (s), 154.3 (s), 137.4 (d), 121.3 (t), 115.0 (t), 37.3 (t), 37.1 (d), 32.4 (d), 32.3 (2t), 31.6 (2t), 28.3 (t), 22.4 (q). MS: 206 (M^+, 4), 191(6), 178(16), 177(44), 151(45), 149(33), 123(23), 110(18), 109(17), 107(14), 105(10), 95(35), 93(21), 81(100), 79(24), 67(42), 55(64), 41(28). **8l** (1st eluted): ^{1}H NMR: δ 5.95 (s, 1H), 5.83 (ddt, J = 17.1, 10.2, 6.5, 1H), 5.65 (d, J = 1.3, 1H), 5.03 (dq, J = 17.1, 1.6, 1H), 4.97 (ddt, J = 10.2, 1.7, 1.3, 1H), 2.77 (m, 2H), 2.60 (ttd, J = 10.4, 3.7, 1.1, 1H), 2.36 (m, 2H), 1.88 (m, 1H), 1.72 (m, 2H), 1.51–1.33 (m, 4H), 1.14–0.99 (m, 2H), 0.96 (d, J = 7.2, 3H). ^{13}C NMR: δ 201.7 (s), 154.2 (s), 137.4 (d), 121.2 (t), 115.0 (t), 37.2 (t), 37.0 (d), 35.1 (2t), 28.3 (t), 27.5 (d), 26.6 (2t), 18.1 (q). MS: 206 (M^+, 7), 192(11), 191(7), 178(19), 177(50), 151(41), 149(35), 133(45), 123(20), 110(27), 109(27), 107(20), 105(24), 95(48), 93(45), 91(25), 81(100), 79(31), 67(46), 55(82), 41(35). IR (**8d + 8l**): ν_{max} 2922vs, 2850s, 1681vs, 1641m, 1448s, 1377m, 997m, 912s. Anal. calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.46; H, 10.68%.

2-Cyclopentylhepta-1,6-dien-3-one (8e). ^{1}H NMR: δ 5.95 (s, 1H), 5.83 (ddt, J = 17.1, 10.3, 6.5, 1H), 5.70 (d, J = 1.5, 1H), 5.04 (dq, J = 17.1, 1.7, 1H), 4.95 (ddt, J = 10.2, 1.8, 1.3, 1H), 2.93 (m, 1H), 2.79 (m, 2H), 2.37 (m, 2H), 1.91–1.82 (m, 2H), 1.74–1.55 (m, 4H), 1.35–1.24 (m, 2H). ^{13}C NMR: δ 201.6 (s), 152.7 (s), 137.3 (d), 120.7 (t), 115.0 (t), 40.0 (d), 37.3 (t), 31.9 (2t), 28.4 (t), 24.8 (2t). MS: 178 (M^+, 1), 163(2), 149(18), 137(5), 123(43), 110(8), 95(100), 83(9), 79(15), 67(73), 55(61), 41(23). IR: ν_{max} 2953vs, 2869s, 1681vs, 1641m, 1414m, 997m, 913s. Anal. calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.03; H, 10.21%.

2-Benzylhepta-1,6-dien-3-one (8g). ^{1}H NMR: δ 7.28–7.10 (m, 5H), 6.03 (s, 1H), 5.78 (ddt, J = 17.1, 10.2, 6.6, 1H), 5.58 (t, J = 1.4, 1H), 4.99 dq (J = 17.1, 1.6, 1H), 4.94 (ddt, J = 10.2, 1.8, 1.3, 1H), 3.58 (s, 2H), 2.74 (m, 2H), 2.32 (dtt, J = 7.8, 6.4, 2.9, 2H). ^{13}C NMR: δ 200.3 (s), 148.2 (s), 139.0 (s), 137.2 (d), 129.0 (2d), 128.3 (2d), 126.1 (d), 125.1 (t), 115.1 (t), 37.0 (t), 36.9 (t), 28.2 (t). MS: 200 (M^+, 10), 199(12), 172(58), 171(22), 159(25), 145(39), 129(19), 117(100), 116(27), 115(73), 91(47), 65(12), 55(18), 38(12). IR: ν_{max} 3028m, 2920m, 1679vs, 1641m, 1494m, 1433m, 1076m, 915s, 744m. HRMS: calcd for $C_{14}H_{16}O$: 200.1201. Found: 200.1198.

(±)-2-[(1′*R,3a*R**,6a*R**)-Octahydropentalen-1-yl]hepta-1,6-dien-3-one (8h).** ^{1}H NMR: δ 5.93 (s, 1H), 5.85 (ddt, J = 17.1, 10.4, 6.4, 1H), 5.67 (dt, J = 5.6, 2.0, 1H), 5.62 (s, 1H), 5.43 (dt, J = 5.6, 2.2, 1H), 5.05 (dq, J = 17.1, 1.6, 1H), 4.98 (d, J = 10.2, 1H), 3.51 (m, 1H), 3.16 (m, 1H), 2.80 (m, 2H), 2.39 (m, 2H), 2.19 (m, 1H), 1.76 (m, 1H), 1.68–1.55 (m, 2H), 1.53–1.39 (m, 3H). ^{13}C NMR: δ 201.0 (s), 152.9 (s), 137.3 (d), 136.6 (d), 130.9 (d), 121.8 (t), 114.9 (t), 53.3 (d), 49.7 (d), 49.5 (d), 37.1 (t), 35.0 (t), 31.5 (t), 28.3 (t), 24.9 (t). MS: 216 (M^+, 3), 201(7), 188(61), 187(100), 175(19), 161(74), 133(24), 131(19), 117(18), 105(53), 91(76), 79(41), 77(30), 65(17), 55(40), 41(17). IR: ν_{max} 3044w, 2946vs, 2863s, 1680vs, 1641m, 1446m, 996m, 912s. Anal. calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.18; H, 9.28%.

***cis*- and *trans*-2-(2-Methylcyclohexyl)hepta-1,6-dien-3-one (8i + 8p).** 62:37 mixture, separated on *DB*^{TM}*-5* column. **8i** (2nd eluted): ^{1}H NMR: δ 6.01 (s, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.51 (d, *J* = 1.3, 1H), 5.04 (dq, *J* = 17.1, 1.7, 1H), 4.97 (ddt, *J* = 10.2, 1.8, 1.4, 1H), 2.86 (dtd, *J* = 12.9, 3.5, 0.9, 1H), 2.86–2.68 (m, 2H), 2.40–2.33 (m, 2H), 1.94 (m, 1H), 1.81–1.24 (m, 8H), 0.69 (d, *J* = 7.3, 3H). ^{13}C NMR: δ 201.5 (s), 152.6 (s), 137.3 (d), 122.2 (t), 114.9 (t), 40.2 (d), 37.3 (t), 32.7 (t), 29.7 (d), 28.3 (t), 26.6 (t), 24.2 (t), 20.1 (t), 12.2 (q). MS: 206 (M^+, 32), 191(15), 178(15), 177(42), 165(27), 164(33), 151(71), 149(41), 133(17), 123(39), 109(29), 95(45), 83(41), 81(100), 79(28), 67(51), 55(86), 53(26), 41(40). HRMS: calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1659. **8p** (1st eluted): ^{1}H NMR: δ 6.05 (s, 1H), 5.84 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.69 (s, 1H), 5.04 (dq, *J* = 17.1, 1.7, 1H), 4.97 (ddt, *J* = 10.2, 1.8, 1.4, 1H), 2.86–2.68 (m, 2H), 2.40–2.33 (m, 2H), 2.31 (td, *J* = 11.4, 3.2, 1H), 1.81–0.98 (m, 9H), 0.71 (d, *J* = 6.4, 3H). ^{13}C NMR: δ 201.2 (s), 153.3 (s), 137.3 (d), 122.6 (t), 114.9 (t), 44.3 (d), 37.0 (t), 36.9 (d), 35.5 (t), 34.3 (t), 28.4 (t), 26.6 (t), 26.4 (t), 20.1 (q). MS: 206 (M^+, 44), 191(16), 178(17), 177(45), 165(29), 164(37), 163(21), 151(76), 149(45), 133(40), 123(38), 109(33), 107(26), 105(26), 95(51), 93(36), 81(95), 79(33), 67(54), 55(100), 53(30), 41(50). HRMS: calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1681. IR (**8i** + **8p**): ν_{max} 2925vs, 2853s, 1681vs, 1641m, 1446m, 1414w, 1047m, 913m.

6-Methyleneundec-1-en-5-one (8j). ^{1}H NMR: δ 5.98 (s, 1H), 5.83 (ddt, *J* = 17.1, 10.4, 6.6, 1H), 5.71 (s, 1H), 5.03 (dq, *J* = 17.1, 1.7, 1H), 4.97 (ddt, *J* = 10.4, 1.8, 1.3, 1H), 2.78 (m, 2H), 2.36 (dtt, *J* = 7.8, 6.6, 1.4, 2H), 2.26 (m, 2H), 1.45–1.23 (m, 6H), 0.88 (t, 3H). ^{13}C NMR: δ 200.8 (s), 148.9 (s), 137.2 (d), 123.2 (t), 114.8 (t), 36.7 (t), 31.4 (t), 30.7 (t), 28.2 (t), 28.0 (t), 22.3 (t), 13.8 (q). MS: 180 (M^+, 1), 165(2), 151(7), 125(26), 123(20), 109(12), 95(20), 81(14), 69(46), 67(11), 55(100), 43(13), 41(25), 39(15). IR: ν_{max} 2957vs, 2928vs, 2859s, 1680vs, 1641m, 1437m, 1368w, 997m, 913s. Anal. calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.74; H, 11.20%.

2-Cyclohexylmethylhepta-1,6-dien-3-one (8k). ^{1}H NMR: δ 6.00 (s, 1H), 5.83 (ddt *J* = 17.2, 10.3, 6.4, 1H), 5.67 (td, *J* = 1.0, 0.8, 1H), 5.04 (dq, *J* = 17.2, 1.7, 1H), 4.98 (ddt, *J* = 10.2, 1.8, 1.3, 1H), 2.78 (m, 2H), 2.36 (dtt, *J* = 7.8, 6.5, 1.4, 2H), 2.16 (dd, 7.0, 0.9, 2H), 1.72–1.55 (m, 5H), 1.35 (m, 1H), 1.25–1.06 (m, 3H), 0.91–0.79 (m, 2H). ^{13}C NMR: δ 201.2 (s), 147.4 (s), 137.4 (d), 124.7 (t), 115.0 (t), 40.0 (t), 36.9 (t), 36.6 (d), 33.1 (2t), 28.4 (t), 26.4 (t), 26.2 (2t). MS: 206 (M^+, 17), 191(3), 177(5), 165(20), 164(23), 151(26), 133(27), 123(46), 109(24), 95(47), 83(27), 81(43), 79(24), 69(33), 67(30), 55(100), 41(55). IR: ν_{max} 2923vs, 2851s, 1680vs, 1641w, 1448m, 997w, 911m. HRMS: calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1671.

6-Methylenenon-1-en-5-one (8n). ^{1}H NMR: δ 5.99 (s, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.72 (td, *J* = 1.3, 0.5, 1H), 5.04 (dq, *J* = 17.1, 1.7, 1H), 4.97 (ddt, *J* = 10.2, 1.9, 1.3, 1H), 2.78 (m, 2H), 2.36 (dtt, *J* = 7.8, 6.6, 1.4, 2H), 2.25 (m, 2H), 1.43 (sx, *J* = 7.6, 2H), 0.91 (t, *J* = 7.6, 3H). ^{13}C NMR: δ 200.9 (s), 148.6 (s), 137.2 (d), 123.4 (t), 114.8 (t), 36.7 (t), 32.8 (t), 28.2 (t), 21.4 (t), 13.6 (q). MS: 152 (M^+, 7), 124(7), 123(40), 110(14), 97(100), 95(16), 81(9), 69(87), 67(12), 55(37), 41(81), 39(20). IR: ν_{max} 3080w, 2961vs, 2932s, 2873s, 1680vs, 1642s, 1414m, 998m, 913s. HRMS: calcd for $C_{10}H_{16}O$: 152.1201. Found: 152.1191.

2-Cyclooctylhepta-1,6-dien-3-one (8o). ^{1}H NMR: δ 5.97 (s, 1H), 5.83 (ddt, *J* = 17.1, 10.3, 6.5, 1H), 5.67 (d, *J* = 1.0, 1H), 5.05 (dq, *J* = 17.1, 1.7, 1H), 4.97 (ddt, *J* = 10.2, 1.8, 1.2, 1H), 2.86 (m, 1H), 2.77 (m, 2H), 2.36 (m, 2H), 1.73–1.39 (m, 14H). ^{13}C NMR: δ 201.2 (s), 155.8 (s), 137.4 (d), 121.5 (t), 114.9 (t), 37.2 (t), 36.9 (d), 32.0 (2t), 28.4 (t), 26.7 (2t), 26.2 (t), 25.6 (2t). MS: 220 (M^+, 4), 205(2), 191(30), 179(19), 177(14), 149(28), 137(15), 135(17), 123(21), 121(24), 109(32), 110(22), 95(94), 81(79), 67(54), 55(100), 41(47). IR: ν_{max} 2920vs, 2851s, 1680vs, 1641m, 1446m, 1045w, 996m, 912m. Anal. calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.78; H, 11.05%.

3-Cyclohexyl-2-methylocta-2,7-dien-4-one (8q). ^{1}H NMR δ 5.86 (ddt, *J* = 17.0, 10.4, 6.6, 1H), 5.07 (dq, *J* = 17.0, 1.6, 1H), 4.99 (ddt, *J* = 10.4, 1.8, 1.3, 1H), 2.59 (m, 2H), 2.44–2.33 (m, 3H), 1.80–1.72 (m, 2H), 1.71–1.62 (m, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.33–1.06 (m, 5H). ^{13}C NMR: δ 210.8 (s), 142.8 (s), 137.5 (d), 127.4 (s), 115.1 (t), 44.8 (t), 39.4 (d), 31.6 (2t), 27.3 (t), 26.7 (2t), 25.9 (t), 22.0 (q), 19.2 (q). MS: 220 (M^+, 5), 205(7), 191(8), 166(12), 165(100), 137(8), 109(12), 95(25), 81(35), 69(52), 55(32), 41(21). IR: ν_{max} 2925vs, 2853s, 1712s, 1694s, 1642w, 1449s, 1377m, 1202m, 996m, 911s. $C_{15}H_{24}O$: 220.1827. Found: 220.1827.

(*E*)-6-Cyclohexylnona-1,6-dien-5-one (8s). Contained 5% of the (*Z*)-isomer. ^{1}H NMR δ 6.35 (t, *J* = 7.3, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 6.5, 1H), 5.03 (dq, *J* = 17.1, 1.7, 1H), 4.96 (ddt, *J* = 10.2, 1.8, 1.2, 1H), 2.70 (m, 2H), 2.51 (tt, *J* = 12.1, 3.4, 1H), 2.32 (m, 2H), 2.28 (q, *J* = 7.5, 2H), 1.83–1.62 (m, 5H), 1.44 (m, 2H), 1.33–1.18 (m, 3H), 1.07 (t, *J* = 7.5, 3H). ^{13}C NMR: δ 202.3 (s), 145.6 (s), 142.3 (d), 137.5 (d), 114.7 (t), 38.4 (d), 37.9 (t), 30.5 (2t), 28.6 (t), 26.9 (2t), 25.8 (t), 21.6 (t), 13.6 (q). MS: 220 (M^+, 10), 191(43), 177(9), 165(100), 149(5), 137(11), 123(7), 109(12), 95(86), 81(72), 79(23), 67(34), 55(63), 41(26). IR: ν_{max} 2927vs, 2852s, 1672s, 1641w, 1450m, 911m. HRMS: calcd for $C_{15}H_{24}O$: 220.1827. Found: 220.1816.

2-Methyl-3-methyleneoct-7-en-4-one (8u). ^{1}H NMR δ 5.97 (s, 1H), 5.84 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.69 (d, *J* = 1.3, 1H), 5.04 (dq, *J* = 17.1, 1.7, 1H), 4.97 (ddt, *J* = 10.2, 1.9, 1.3, 1H), 2.92 (spd, *J* = 6.8, 1.0, 1H), 2.7 (m, 2H), 2.37 (dtt, *J* = 8.0, 6.6, 1.4, 2H), 1.02 (d, *J* = 6.8, 6H). ^{13}C NMR: δ 201.2 (s), 155.2 (s), 137.3 (d), 120.8 (t), 115.0 (t), 37.3 (t), 28.4 (t), 27.7 (d), 21.8 (2q). MS: 152 (M^+, 3), 137(34), 123(13), 109(14), 97(84), 83(13), 69(100), 55(62), 53(22), 43(12), 41(98), 39(32), 27(17). IR: ν_{max} 2963vs, 2873m, 1681vs, 1641s, 1464m, 1368s, 998m, 914s. Anal. calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.73; H, 10.61%.

6-Methylenedodec-1-en-5-one (8v). ^{1}H NMR δ 5.98 (s, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.71 (s, 1H), 5.03 (dq, *J* = 17.1, 1.7, 1H), 4.97 (ddt, *J* = 10.2, 1.8, 1.3, 1H), 2.78 (m, 2H), 2.36 (dtt, *J* = 7.8, 6.4, 1.4, 2H), 2.26 (m, 2H), 1.44–1.20 (m, 8H), 0.88 (t, *J* = 7.0, 3H). ^{13}C NMR: δ 200.8 (s), 149.0 (s), 137.2 (d), 123.2 (t), 114.8 (t), 36.8

(t), 31.5 (t), 30.7 (t), 28.8 (t), 28.3 (t), 28.2 (t), 22.4 (t), 13.8 (q). MS: 194 (M$^+$, 1), 179(2), 165(4), 151(8), 139(21), 123(24), 110(12), 109(19), 95(25), 83(11), 81(14), 69(100), 67(17), 55(66), 43(18), 41(34), 29(13). IR: ν_{max} 2956vs, 2927vs, 2857s, 1680vs, 1641m, 1437m, 1114w, 997m, 913s. Anal. calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.53; H, 11.25%.

8,8-Dimethyl-6-methylenenon-1-en-5-one (8w). ^{1}H NMR δ 6.05 (d, J=0.5, 1H), 5.84 (ddt, J=17.1, 10.4, 6.6, 1H), 5.66 (m, 1H), 5.05 (dq, J=17.1, 1.7, 1H), 4.98 (ddt, J=10.3, 1.8, 1.3, 1H), 2.80 (m, 2H), 2.37 (m, 2H), 2.28 (d, J=0.6, 2H), 0.83 (s, 9H).). ^{13}C NMR: δ 201.3 (s), 147.1 (s), 137.3 (d), 125.8 (t), 114.9 (t), 43.1 (t), 36.8 (t), 31.1 (s), 29.2 (3q), 28.3 (t). MS: 180 (M$^+$, 2), 165(9), 125(16); 124(20), 109(23), 96(26), 95(68), 81(16), 68(17), 57(100), 55(25), 41(31). IR: ν_{max} 2953s, 2867w, 1682vs, 1642w, 1476w, 1365s, 1154m, 997m, 912s. HRMS: calcd for $C_{12}H_{20}O$: 180.1514. Found: 180.1506.

(1′*R*/*S*=2:1)-*cis*-2-(2,2,3-Trimethylcyclopentyl)hepta-1,6-dien-3-one (8x). Contained 10% of the *trans*-isomer. ^{1}H NMR δ 6.13 (s, 1H), 5.84 (ddt, J=17.1, 10.4, 6.4, 1H), 5.67 (d, J=0.6, 1H), 5.05 (dq, J=17.1, 1.7, 1H), 4.98 (ddt, J=10.2, 1.8, 1.3, 1H), 3.09 (dd, J=11.8, 8.6, 1H), 2.88 (dt, J=16.9, 7.5, 1H), 2.75 (dt, J=16.9, 7.5, 1H), 2.38 (m, 2H), 1.84 (m, 1H), 1.77–1.56 (m, 3H), 1.27 (m, 1H), 0.85 (d, J=6.7, 3H), 0.72 (s, 3H), 0.48 (s, 3H). ^{13}C NMR: δ 202.2 (s), 149.2 (s), 137.4 (d), 123.6 (t), 115.1 (t), 48.3 (d), 45.3 (d), 43.2 (s), 37.5 (t), 29.7 (t), 28.5 (t), 27.0 (t), 26.2 (q), 15.2 (q), 14.4 (q). MS: 220 (M$^+$, 6), 205(16), 177(19), 165(39), 163(33), 149(26), 137(47), 121(30), 109(49), 107(29), 95(64), 84(42), 83(40), 81(77), 79(32), 69(89), 55(100), 53(39), 41(54). IR: ν_{max} 2958vs, 2871s, 1683vs, 1641w, 1468m, 1368m, 1208w, 997m, 912s. Anal. calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.94; H, 10.78%.

(*R*/*S*=2:1)-2-(2,2,3-Trimethylcyclopent-3-enyl)hepta-1,6-dien-3-one (8y). ^{1}H NMR δ 6.12 (s, 1H), 5.85 (ddt, J=17.1, 10.2, 6.6, 1H), 5.78 (d, J=0.8, 1H), 5.29 (m, 1H), 5.05 (dq, J=17.1, 1.7, 1H), 4.99 (ddt, J=10.2, 1.8, 1.4, 1H), 3.39 (td, J=8.1, 0.9, 1H), 2.87 (dt, J=16.9, 7.5, 1H), 2.78 (ddd, J=16.9, 7.8, 6.8, 1H), 2.39 (m, 2H), 2.37–2.20 (m, 2H), 1.59 (m, 3H), 1.00 (s, 3H), 0.67 (s, 3H). ^{13}C NMR: δ 202.0 (s), 150.2 (s), 147.1 (s), 137.4 (d), 123.6 (t), 121.4 (d), 115.1 (t), 48.1 (s), 47.9 (d), 37.3 (t), 34.9 (t), 28.5 (t), 26.6 (q), 21.5 (q), 12.8 (q). MS: 218 (M$^+$, 20), 203(44), 177(26), 163(21), 161(65), 147(27), 135(38), 133(26), 121(35), 119(70), 109(31), 108(52), 107(48), 105(97), 93(77), 91(68), 79(43), 77(44), 55(100), 41(39). IR: ν_{max} 3038w, 2957vs, 2932s, 2853m, 1682vs, 1641m, 1437m, 1361m, 997m, 913s. Anal. calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.67; H, 10.18%.

7,9,9-Trimethyl-6-methylenedec-1-en-5-one (8z). ^{1}H NMR δ 6.00 (s, 1H), 5.84 (ddt, J=17.2, 10.2, 6.6, 1H), 5.75 (d, J=0.8, 1H), 5.04 (dq, J=17.2, 1.6, 1H), 4.98 (ddt, 10.2, 1.8, 1.3, 1H), 2.94 (m, 1H), 2.78 (m, 2H), 2.37 (m, 2H), 1.49 (dd, J=14.0, 6.7, 1H), 1.25 (dd, J=14.0, 5.2, 1H), 1.03 (d, J=7.0, 3H), 0.86 (s, 9H). ^{13}C NMR: δ 200.9 (s), 156.2 (s), 137.4 (d), 122.3 (t), 115.0 (t), 50.5 (t), 37.3 (t), 31.2 (s), 30.0 (3q), 29.6 (d), 28.4 (t), 23.9 (q). MS: 208 (M$^+$, 1), 193(20), 179(7), 153(41), 151(32), 137(64), 123(40), 109(40), 97(25), 95(30), 83(50), 69(48), 67(26), 57(100), 55(87), 43(28), 41(47). IR: ν_{max} 2956vs, 2906s, 2869s, 1679vs, 1642m, 1476m, 1364s, 927m, 913s. Anal. calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.69; H, 11.59%.

(*E*)-2-Cyclohexylbut-2-enal (14b). A mixture of [(2-cyclohexylethenyl)oxy)]trimethylsilane[38] (19.8 g, 0.1 mol) and acetaldehyde (4.4 g, 0.1 mol) was added slowly at −70 °C to a solution of titanium (IV) chloride (11 mL, 0.1 mol) and titanium (IV) isopropoxide (0.59 mL, 0.02 mol) in CH_2Cl_2 (50 mL). After stirring for 1 h at −70 °C the reaction was quenched with saturated NH_4Cl soln and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with water to neutral pH, dried ($MgSO_4$) and concentrated in vacuo. The crude aldol was dehydrated by distillation (120 °C/0.1 torr) in the presence of I_2 (0.2 g) using a 5 cm Widmer column to give **14b**[39] that contained ~12% of its (*Z*)-isomer (7.7 g, 50%). ^{1}H NMR: δ 9.31 (d, J=1.5, 1H), 6.46 (q, J=7.2, 1H), 2.54 (ttd, J=12.1, 3.5, 1.5, 1H), 2.01 (d, J=7.2, 3H), 1.88–1.61 (m, 5H), 1.49–1.41 (m, 2H), 1.39–1.02 (m, 3H). ^{13}C NMR: δ 195.6 (d), 150.3 (d), 148.2 (s), 36.4 (d), 29.7 (2t), 26.8 (2t), 25.9 (t), 15.0 (q). MS: 152 (M$^+$, 72), 137(29), 134(14), 123(100), 119(24), 109(43), 105(25), 95(57), 91(37), 84(21), 81(68), 79(45), 77(24), 69(31), 67(72), 55(48), 41(50). IR: ν_{max} 2927vs, 2853s, 2704w, 1689vs, 1634m, 1450m, 1213m, 1008w, 892m, 831m.

***cis*- and *trans*-2-(2-Methylcyclopentyl)acrylonitrile (13c+13m).** The methodology of Stetter and Kuhlmann[40] for preparation of α-alkylacrylates was adapted. KOH (16.3 g, 0.29 mol) in EtOH (200 mL) was added at room temperature during 1 h to a solution of ethyl cyano(2-methylcyclopentyl)acetate (56.5 g, 0.29 mol), obtained as a 34:32:20:13 diast. rac. mixture according to Herz,[41] in EtOH (200 mL). The reaction mixture was stirred at room temperature for 18 h, concentrated at 70 °C/75 torr and dissolved in water (250 mL). Concd HCl (250 mL) was added dropwise at 10 °C under vigorous stirring and the mixture was extracted with MTBE (500 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo and reacted with paraformaldehyde (7.2 g), pyridine (46 mL) and piperidine (2.5 g, 29 mmol) at 130 °C for 3 h. After cooling, the reaction mixture was poured into ice/water, and extracted with MTBE (2 × 200 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and distilled using a 5 cm Vigreux column (31 °C/0.08 torr) to give a 3:2 mixture of **13c**+**13m** (22.5 g, 58%). **13c**: ^{1}H NMR: δ 5.90 (t, J=0.9, 1H), 5.68 (dd, J=1.3, 0.6, 1H), 2.69 (m, 1H), 2.28 (m, 1H, 1.90–1.79 (m, 3H), 1.75 (m, 1H), 1.60 (m, 1H), 1.24 (m, 1H), 0.89 (d, J=7.1, 3H). ^{13}C NMR: δ 130.0 (t), 125.3 (s), 119.2 (s), 47.9 (d), 37.1 (d), 33.2 (t), 27.9 (t), 23.0 (t), 15.6 (q). MS: 135 (M$^+$, 15), 134(21), 120(20), 107(20), 106(27), 93(16), 80(100), 66(15), 56(94), 55(16), 53(20), 41(45), 39(25). HRMS: calcd for $C_9H_{13}N$: 135.1048. Found: 135.1039. **13m**: ^{1}H NMR: δ 5.81 (d, J=0.9, 1H), 5.71 (t, J=0.7, 1H), 2.08 (m, 1H), 1.99–1.79 (m, 3H), 1.76–1.63 (m, 3H), 1.24 (m, 1H), 0.98

(d, $J=6.4$, 3H). ^{13}C NMR: δ 129.5 (t), 126.9 (s), 117.8 (s), 53.1 (d), 39.7 (d), 34.1 (t), 31.7 (t), 23.3 (t), 18.0 (q). MS: 135 (M^+, 13), 134(16), 120(21), 107(20), 106(19), 93(17), 80(100), 66(17), 56(94), 53(19), 41(41), 39(24). HRMS: calcd for $C_9H_{13}N$: 135.1048. Found: 135.1036. IR (**13c**+**13m**): ν_{max} 2959vs, 2873s, 2221w, 1618w, 1458m, 1405w, 1379w, 936m.

***cis*- and *trans*-2-(2-Methylcyclopentyl)propenal (14c+14m).** 1 M solution of DIBAH in hexane (200 mL, 0.2 mol) was added dropwise to **13c** (13.5 g, 0.1 mol) in toluene (200 mL) at −73 °C. The reaction mixture was stirred for 1 h at the same temperature, poured into ice-cold 5% H_2SO_4 (300 mL) and extracted with MTBE (300 mL). The extract was dried ($MgSO_4$) and the solvents evaporated under reduced pressure to give a 3:2 mixture of **14c**+**14m** (7.1 g, 51%) as yellowish oil used in the next step without further purification. **14c**: ^{1}H NMR: δ 9.55 (s, 1H), 6.20 (s, 1H), 6.07 (s, 1H), 2.95 (m, 1H), 2.37 (m, 1H), 1.90 (m, 1H), 1.80–1.51 (m, 4H), 1.30 (m, 1H), 0.57 (d, $J=7.1$, 3H). ^{13}C NMR: δ 195.1 (d), 151.6 (s), 134.0 (t), 41.5 (d), 34.7 (d), 33.3 (t), 27.5 (t), 22.6 (t), 16.4 (q). MS: 138 (M^+, 29), 123(27), 110(17), 109(100), 95(74), 83(32), 81(50), 79(29), 67(70), 55(38), 53(32), 41(60), 39(42). HRMS: calcd for $C_9H_{14}O$: 138.1045. Found: 138.1036. **14m**: ^{1}H NMR: δ 9.56 (s, 1H), 6.25 (s, 1H), 5.99 (s, 1H), 2.41 (m, 1H), 2.05–1.83 (m, 3H), 1.74–1.62 (m, 2H), 1.42 (m, 1H), 1.27 (m, 1H), 0.92 (d, $J=6.2$, 3H). ^{13}C NMR: δ 195.1 (d), 153.4 (s), 132.9 (t), 45.6 (d), 39.6 (d), 34.4 (t), 32.9 (t), 23.6 (t), 18.6 (q). MS: 138 (M^+, 35), 123(42), 110(18), 109(100), 105(19), 95(58), 83(25), 81(47), 79(27), 67(73), 55(33), 53(28), 41(52), 39(38). HRMS: calcd for $C_9H_{14}O$: 138.1045. Found: 138.1031. IR (**14c**+**14m**): ν_{max} 2955vs, 2870s, 2696w, 1695vs, 1624w, 1456m, 1377w, 1245w, 940m.

2-Cyclohexyl-3-methylbut-2-enal (14q). Ethyl cyclohexylacetate (25.5 g, 0.15 mol) in abs THF (25 mL) and HMPA (50 mL) was added to a 1.6 M THF solution of LDA (92 mL, 0.15 mol) at −65 °C. After 20 min of stirring, acetone (8.7 g, 0.15 mol) in THF (10 mL) was added and stirring continued for additional 4 h at −65 °C, and overnight in the ice/NaCl bath. The reaction mixture was poured into ice-cold 2 N HCl, extracted (Et_2O) dried ($MgSO_4$) and concentrated in vacuo. The crude ethyl 2-cyclohexyl-3-hydroxy-3-methylbutyrate was distilled, reduced with LAH and oxidised (MnO_2) as usual to give a crude mixture of **14q** (unstable) and 2-cyclohexyl-3-hydroxy-3-methylbutanal used without purification in the next step.

2-Cyclopentylhepta-1,6-dien-3-ol (15e). Prepared in a similar manner as **15a** starting from cyclopentylacetaldehyde: ^{1}H NMR δ 5.85 (ddt, $J=17.1$, 10.4, 6.6, 1H), 5.05 (ddt, $J=17.1$, 2.0, 1.6, 1H), 5.03 (t, $J=1.0$, 1H), 4.98 (ddt, $J=10.3$, 2.0, 1.1, 1H), 4.93 (t, $J=1.0$, 1H), 4.13 (dd, $J=7.6$, 4.8, 1H), 2.38 (ttd, $J=9.7$, 7.3, 0.8, 1H), 2.25–2.06 (m, 2H), 1.91–1.81 (m, 2H), 1.77–1.51 (m, 7H), 1.49–1.28 (m, 2H). ^{13}C NMR: δ 156.4 (s), 138.5 (d), 114.8 (t), 107.4 (t), 74.6 (d), 42.2 (d), 35.1 (t), 33.2 (t), 32.9 (t), 30.1 (t), 25.0 (2t). MS: 179 ($[M-H]^+$, 0.5), 162(5), 151(8), 133(10), 126(13), 125(21), 111(38), 107(22), 97(30), 95(37), 93(37), 91(36), 83(70), 81(36), 79(57), 67(66), 55(100), 43(31), 41(10), 39(25). IR: ν_{max} 3359s, 3077w, 2952vs, 2869s, 1641m, 1451m, 1059m, 904s. Anal. calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.96; H, 11.10%.

General procedure for the synthesis of hepta-1,6-dien-3-ones 8

Method B; via cyanohydrins 11. 2-Cycloheptyl-3-hydroxypropionitrile (11f). A solution of crude ethyl cyanocycloheptylacetate[42] (47.5 g, 0.23 mol), prepared in a similar way as the starting material in the synthesis of **13c**, in EtOH (200 mL) was added dropwise during 1 h into a suspension of $NaBH_4$ (7.44 g, 0.20 mol) in the same solvent (50 mL) at 0 °C and stirring continued for 18 h at room temperature. The reaction mixture was concentrated in vacuo, diluted with MTBE (300 mL), washed successively with ice/water (300 mL), 1 N HCl (200 mL) and brine (2 × 300 mL) and dried ($MgSO_4$). Evaporation of solvents under reduced pressure gave **11f** (34.8 g, 91%) used in the next step without further purification. ^{1}H NMR δ 3.85 (dd, $J=10.9$, 7.6, 1H), 3.78 (dd, $J=10.9$, 5.7, 1H), 2.71 (dt, $J=7.6$, 5.7, 1H), 2.14 (m broad, 1H), 1.91–1.66 (m, 5H), 1.65–1.37 (m, 8H).). ^{13}C NMR: δ 120.4 (s), 61.3 (t), 42.3 (d), 37.9 (d), 33.1 (t), 31.0 (t), 27.9 (t), 27.8 (t), 26.3 (t), 26.2 (t). MS: 166 ($[M-H]^+$, 0.2), 148(2), 136(6), 122(5), 108(23), 97(92), 94(19), 81(20), 80(29), 67(17), 55(100), 41(25). IR: ν_{max} 3442s, 2926vs, 2856s, 2241w, 1461m, 1052m. HRMS: $[M-H]^+$ calcd for $C_{10}H_{16}NO$: 166.1232. Found: 166.1202.

2-Cycloheptyl-3-trimethylsilyloxypropionitrile (12f). First triethylamine (24.35 g, 0.24 mol), then chlorotrimethylsilane (26.2 g, 0.24 mol) was added to a solution of **11f** (33.4 g, 0.20 mol) in THF (350 mL) at −5 to 0 °C. After additional 4 h stirring at room temperature, the precipitate was filtered off and the reaction mixture concentrated in vacuo, diluted with hexane (300 mL) and washed successively with 1 N HCl, (100 mL), aqueous sodium bicarbonate solution (100 mL) and brine (2 × 200 mL) and dried ($MgSO_4$). After evaporation of solvents under reduced pressure, pure **12f** (47.1 g, 98%) was obtained. ^{1}H NMR δ 3.76 (dd, $J=10.1$, 7.3, 1H), 3.70 (dd, $J=10.1$, 6.4, 1H), 2.65 (ddd, $J=7.2$, 6.3, 4.8, 1H), 1.89–1.67 (m, 5H), 1.65–1.39 (m, 8H), 0.14 (s, 9H). ^{13}C NMR: δ 120.4 (s), 61.1 (t), 42.2 (d), 37.6 (d), 33.3 (t), 30.5 (t), 28.0 (t), 27.8 (t), 26.5 (t), 26.2 (t), −0.6 (3q). MS: 239 (M^+, 0.04), 225(16), 224(100), 209(19), 194(16), 152(8), 121(9), 103(29), 101(12), 75(16), 73(44), 55(13). IR: ν_{max} 2927vs, 2857s, 2240w, 1461m, 1252s, 1112s, 874s, 844vs, 751m. HRMS: $[M-CH_3]^+$ calcd for $C_{12}H_{22}NSiO$: 224.1471. Found: 224.1463.

2-Cycloheptylhepta-1,6-dien-3-one (8f). 4-Bromobut-1-ene (36.5 g, 0.27 mol) in toluene (200 mL) was added to magnesium turnings (6.0 g, 0.25 mol) suspended in gently refluxing Et_2O (35 mL). After additional 1 h stirring at 70 °C, a solution of **12f** (38.3 g, 0.16 mol) in toluene (160 mL) was slowly added at the same temperature and stirring continued for 20 h at 75–80 °C. After cooling down to room temperature, concd HCl

(50 mL) was added dropwise and the reaction mixture was concentrated (280 mL of liquids were distilled off through a short Vigreux column), stirred at 110 °C for 3 h, cooled down to room temperature, poured onto ice (250 g) and extracted with MTBE (2 × 250 mL). The combined organic phases were washed successively with 2 N HCl (200 mL), saturated sodium bicarbonate solution (200 mL) and brine (2 × 200 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was flash-distilled and the resulting brown liquid (15.8 g) was fractionated using a 5 cm Vigreux column (88–90 °C/0.07 torr) to give **8f** (9.3 g, 28%). ^{1}H NMR: δ 5.95 (s, 1H), 5.84 (ddt, J = 17.0, 10.2, 6.6, 1H), 5.68 (d, J = 1.0, 1H), 5.04 (dq, J = 17.0, 1.7, 1H), 4.98 (ddt, J = 10.2, 1.7. 1.4, 1H), 2.77 (m, 3H), 2.36 (dtt, J = 7.8, 6.5, 1.4, 2H), 1.77–1.41 (m, 10H), 1.40–1.28 (m, 2H). ^{13}C NMR: δ 201.3 (s), 155.8 (s), 137.4 (d), 121.3 (t), 115.0 (t), 39.3 (d), 37.2 (t), 34.7 (2t), 28.5 (t), 27.8 (2t), 26.9 (2t). MS: 206 (M^+, 3), 191(2), 177(26), 165(9), 151(37), 149(22), 121(13), 109(21), 95(29), 81(100), 79(28), 69(20), 67(56), 55(97), 53(31), 41(52), 39(27). IR: ν_{max} 2924vs, 2855vs, 1680vs, 1641m, 1460m, 1445m, 997m, 912m. Anal. calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.70; H, 10.80%.

***cis*- and *trans*-2-(3-Methylcyclohexyl)hepta-1,6-dien-3-one (8r + 8t).** Prepared according to the general procedure, method B; 2:3 mixture, separated on DB^{TM}-*1* column. **8r** (1st eluted): ^{1}H NMR: δ 5.96 (s, 1H), 5.83 (ddt, J = 17.0, 10.4, 6.5, 1H), 5.65 (d, J = 1.1, 1H), 5.03 (dq, J = 17.0, 1.7, 1H), 4.97 (ddt, J = 10.4, 1.8, 1.3, 1H), 2.77 (m, 2H), 2.61 (tt, J = 11.9, 2.6, 1H), 2.36 (m, 2H), 1.80–1.61 (m, 4H), 1.49 (m, 1H), 1.39 (m, 1H), 1.14 (m, 1H), 0.88 (d, J = 6.6, 3H), 0.84 (m, 1H), 0.74 (q, J = 12.1, 1H). ^{13}C NMR: δ 201.5 (s), 154.3 (s), 137.3 (d), 121.2 (t), 115.0 (t), 41.2 (t), 37.3 (d), 37.3 (t), 34.9 (t), 32.8 (d), 32.0 (t), 28.4 (t), 26.3 (t), 22.7 (q). MS: 206 (M^+, 4), 191(6), 178(11), 177(29), 163(16), 151(47), 123(20), 110(21), 109(15), 95(33), 81(100), 79(22), 67(42), 55(61), 41(28). **8t** (2nd eluted): ^{1}H NMR: δ 5.97 (s, 1H), 5.83 (ddt, J = 17.0, 10.4, 6.5, 1H), 5.66 (d, J = 1.2, 1H), 5.03 (dq, J = 17.0, 1.7, 1H), 4.97 (ddt, J = 10.4, 1.8, 1.3, 1H), 2.88 (tt, J = 10.5, 3.4, 1H), 2.77 (m, 2H), 2.36 (m, 2H), 1.98 (m, 1H), 1.72–1.31 (m, 7H), 1.02 (d, J = 7.2, 3H), 1.00 (m, 1H). ^{13}C NMR: δ 201.7 (s), 154.3 (s), 137.3 (d), 121.3 (t), 115.0 (t), 37.9 (t), 37.4 (t), 32.1 (t), 32.0 (t), 31.5 (d), 28.4 (t), 27.8 (d), 21.0 (t), 18.5 (q). MS: 206 (M^+, 5), 191(13), 178(22), 177(60), 163(40), 151(39), 149(21), 133(31), 123(27), 110(21), 109(35), 107(28), 105(28), 95(69), 93(61), 91(29), 81(100), 79(39), 67(51), 55(98), 41(45). IR (**8r** + **8t**): ν_{max} 2923vs, 2850s, 1681vs, 1641m, 1458m, 1446m, 997m, 913s. Anal. calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.40; H, 10.74%.

2-Cyclohexylhept-1-en-3-one (18). Prepared according to the method A of the general procedure for the synthesis of hepta-1,6-dien-3-ones **8**, using bromobutane instead of 4-bromobut-1-ene. ^{1}H NMR δ 5.94 (s, 1H), 5.62 (d, J = 1.1, 1H), 2.66 (t, J = 7.5, 2H), 2.57 (ttd, J = 11.9, 3.1, 0.8, 1H), 1.80–1.65 (m, 5H), 1.59 (m, 2H), 1.41–1.28 (m, 4H), 1.24–1.13 (m, 1H), 1.07 (m, 2H), 0.92 (t, J = 7.3, 3H). ^{13}C NMR: δ 202.2 (s), 154.4 (s), 120.7 (t), 37.7 (t), 37.4 (d), 32.4 (2t), 26.6 (t), 26.4 (2t), 26.1 (t), 22.2 (t), 13.7 (q). MS: 194 (M^+, 19), 152(10), 151(19), 137(100), 112(12), 109(64), 85(11), 81(19), 79(12), 67(82), 57(20), 55(22), 41(39), 29(19). IR: ν_{max} 2927vs, 2853s, 1680s, 1449m, 1032w, 930m. HRMS: calcd for $C_{13}H_{22}O$: 194.1671. Found: 194.1660.

2-Cyclohexylhept-6-en-3-one (21). Prepared following the method A of the general procedure for the synthesis of hepta-1,6-dien-3-ones **8** starting from 2-cyclohexylpropanal (**19**) obtained by catalytic (Pd/C) hydrogenation of **14a** according to Marshall et al.[43] ^{1}H NMR δ 5.81 (ddt, J = 17.1, 10.2, 6.6, 1H), 5.03 (dq, J = 17.1, 1.7, 1H), 4.96 (ddt, J = 10.2, 1.8, 1.3, 1H), 2.52 (m, 2H), 2.39–2.27 (m, 3H), 1.77–1.51 (m, 6H), 1.30–1.09 (m, 3H), 1.08–0.96 (m, 1H), 1.00 (d, J = 7.0, 3H), 0.96–0.85 (m, 1H). ^{13}C NMR: δ 213.8 (s), 137.2 (d), 114.8 (t), 51.9 (d), 41.1 (t), 39.9 (d), 31.6 (t), 29.1 (t), 27.4 (t) 26.2 (t), 26.1 (2t), 13.0 (q). MS: 194 (M^+, 1), 151(1), 139(9), 113(11), 112(100), 111(67), 97(20), 83(36), 70(15), 69(81), 56(16), 55(82), 41(26). IR: ν_{max} 2925vs, 2852vs, 1711vs, 1641m, 1449s, 1373m, 996m, 911m. Anal. calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.42; H, 11.43%.

(1′*R*/*S* = 2:1)-1-(2,2,3-Trimethylcyclopent-3-enyl)cyclopropanecarbaldehyde (22a). DMSO (700 mL) was added dropwise during 50 min to the mixture of trimethylsulfoxonium iodide (132.0 g, 0.6 mol) and sodium hydride (14.5 g, 0.6 mol) at 10–15 °C. After 2 h of additional stirring at room temperature the hydrogen evolution ceased and 2,2,3-trimethyl-α-methylene-3-cyclopentene-1-acetaldehyde[44] (**14y**, 100.0 g, 0.6 mol), prepared in a similar manner as **14a** starting from α-campholenal (**9y**; *R*/*S* = 1:2), in DMSO (150 mL) was added during 2 h at 8–10 °C. The reaction mixture was poured into a mixture of ice/water and extracted with MTBE (1 L). The extract was washed with brine (3 × 500 mL), dried ($MgSO_4$), concentrated in vacuo and distilled using a Vigreux column (76–79 °C/0.2 torr) to give **22a** (62 g, 58%). ^{1}H NMR δ 9.52 (s, 1H), 5.26 (m, 1H), 2.41–2.31 (m, 1H), 2.24–2.15 (m, 1H), 2.11 (dd, J = 8.5, 7.8, 1H), 1.61 (m, 3H), 1.21 (m, 1H), 1.18 (m, 1H), 1.10 (s, 3H), 0.95 (s, 3H), 0.93–0.89 (m, 2H). ^{13}C NMR: δ 203.3 (d), 148.1 (s), 121.1 (d), 51.2 (d), 48.7 (s), 33.2 (t), 32.3 (s), 28.3 (q), 22.4 (q), 15.2 (t), 14.6 (t), 12.4 (q). MS: 178 (M^+, 71), 163(100), 149(23), 145(26), 135(67), 121(79), 119(78), 108(41), 107(63), 105(39), 95(47), 93(75), 91(69), 81(28), 79(50), 77(40), 55(37), 41(59), 39(32). IR: ν_{max} 3038w, 2958vs, 2932s, 2868m, 1713vs, 1465m, 1361m, 1023w, 896w, 800w. HRMS: calcd for $C_{12}H_{18}O$: 178.1358. Found: 206.1362.

(1′*R*/*S* = 2:1)-1-[1-(2,2,3-Trimethylcyclopent-3-enyl)cyclopropyl]pent-4-en-1-one (24a). Prepared according to the method A of the general procedure for the synthesis of hepta-1,6-dien-3-ones **8** starting from **22a**. ^{1}H NMR: δ 5.80 (ddt, J = 17.1, 10.2, 6.6, 1H), 5.18 (m, 1H), 5.03 (dq, J = 17.1, 1.7, 1H), 4.96 (ddt, J = 10.2, 1.9, 1.3, 1H), 2.89 (t, J = 8.8, 1H), 2.55–2.41 (m, 2H), 2.38–2.24 (m, 2H), 2.10 (m, 1H), 1.76 (m, 1H), 1.57 (dt, J = 2.3, 1.7, 3H), 1.41 (ddd, J = 9.8, 6.6, 5.4, 1H), 1.05 (s, 3H), 0.88 (ddd, J = 9.0, 6.4, 5.4, 1H), 0.85 (s, 3H), 0.73 (ddd, J = 9.0, 6.4, 4.7, 1H), 0.62 (ddd, J = 9.8, 6.6, 4.7, 1H).

^{13}C NMR: δ 209.5 (s), 148.1 (s), 137.5 (d), 120.5 (d), 115.1 (t), 49.0 (s), 48.8 (d), 37.0 (t), 32.1 (s), 31.5 (t), 28.4 (t), 28.0 (q), 21.9 (q), 12.5 (q), 12.3 (t), 9.4 (t). MS: 232 (M$^+$, 30), 217(51), 191(72), 177(23), 161(19), 149(23), 135(37), 134(21), 133(34), 121(47), 119(53), 109(38), 108(99), 107(48), 105(44), 93(66), 91(67), 83(36), 81(36), 79(45), 77(40), 67(23), 55(100), 41(43). IR: ν_{max} 2958vs, 2866m, 1693vs, 1641m, 1465m, 1362s, 1179m, 1074m, 994m, 913s, 800m. Anal. calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.69; H, 10.42%.

1-(1-Cyclohexylcyclopropyl)pent-4-en-1-one (24b). Prepared in a similar manner as **24a** starting from **14a**. ^{1}H NMR δ 5.79 (m, 1H), 5.01 (m, 1H), 4.95 (m, 1H), 2.30 (m, 4H), 1.85 (tt, *J* = 11.9, 3.3, 1H), 1.77–1.61 (m, 3H), 1.59–1.51 (m, 2H), 1.33–0.95 (m, 7H), 0.83–0.76 (m, 2H). ^{13}C NMR: δ 209.8 (s), 137.5 (d), 115.0 (t), 38.1 (d), 36.4 (s), 36.1 (t), 29.9 (2t), 28.4 (t), 26.6 (2t), 26.3 (t), 11.8 (2t). MS: 206 (M$^+$, 6), 177(22), 163(21), 151(100), 123(23), 109(18), 95(18), 83(21), 81(82), 79(23), 67(49), 55(84), 41(42). 39(22). IR: ν_{max} 3078w, 2926vs, 2852s, 1721m, 1687vs, 1641w, 1450m, 1358m, 1068m, 996m, 910m. HRMS: calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1667.

General procedure for the synthesis of 1-cycloalkenylpent-4-en-1-ones 7 and 28

2-Ethynyldecahydronaphthalen-2-ol (26a). Acetylene was bubbled for 4 h through a solution of ^{t}BuOK (95.8 g, 0.85 mol) in THF (1 L) at 0 °C. 2-Decalone (100 g, 0,66 mol, 4:1 *cis*/*trans* mixture) was added slowly at room temperature and the reaction mixture was stirred for additional 3.5 h, quenched with saturated NH$_4$Cl (500 mL) and extracted with MTBE (2 × 700 mL). The combined organic layers were washed with NH$_4$Cl (0.5 L), H$_2$O (2 × 500 mL) and saturated NaCl (500 mL), dried (MgSO$_4$) and concentrated in vacuo. The residue was flash distilled (88–90 °C/0.01 torr) to give **26a** (101 g, 86%) as a 17:8 *cis*/*trans* mixture. ^{1}H NMR *cis*-isomer: δ 2.49 (s, 1H), 2.25 (bs, 1H), 2.04 (m, 1H), 1.88 (t, *J* = 12.5, 1H), 1.83–1.48 (m, 11H), 1.46–1.20 (m, 3H); *trans*-isomer: δ 2.49 (s, 1H), 2.25 (bs, 1H), 2.01 (m, 1H), 1.89 (m, 1H), 1.68–1.48 (m, 4H), 1.39–1.16 (m, 7H), 1.05–0.80 (m, 3H). ^{13}C NMR *cis*: δ 87.5 (s), 72.5 (d), 70.2 (s), 39.6 (t), 35.4 (t), 34.9 (d), 33.6 (d), 31.6 (t), 29.3 (t), 26.5 (t), 25.6 (t), 21.1 (t); *trans*: δ 87.7 (s), 72.5 (d), 69.4 (s), 47.1 (t), 42.4 (d), 40.2 (d), 40.0 (t), 33.3 (t), 33.0 (t), 31.1 (t), 26.5 (t), 26.2 (t). MS *cis*: 178 (M$^+$, 0.4), 177(0.8), 163(6), 160(6), 152(16), 149(43), 145(16), 131(21), 121(38), 110(42), 108(44), 97(51), 95(65), 82(46), 81(88), 79(49), 67(79), 55(100), 53(59), 41(69), 39(50); *trans*: 178 (M$^+$, 0.9), 177(1), 163(8), 160(5), 152(15), 149(46), 145(10), 135(28), 121(69), 110(62), 108(45), 97(48), 95(72), 82(77), 81(92), 79(51), 67(849), 55(100), 53(63), 41(73), 39(51). IR *cis*/*trans* mixture: ν_{max} 3380m, 3307s, 2922vs, 2856s, 1446m, 1276w, 1055m, 1030m, 1007w, 948w. Anal. calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.47; H, 10.32%.

(±)-*cis*-1-(1, 4, 4a, 5, 6, 7, 8, 8a-Octahydronaphthalen-2-yl)pent-4-ene-1-one (7a). A solution of **26a** (101 g, 0.56 mol) in *i*-PrOH (300 mL) was added slowly under nitrogen at 0 °C to a mixture of KOH (47.5 g, 0.85 mol), K$_2$CO$_3$ (6.5 g, 0.047 mol) and CuCl (4.4 g, 0.044 mol) in MeOH (300 mL) and the reaction mixture was stirred for additional 0.5 h at 0 °C. Allyl bromide (102 g, 0.85 mol) was added slowly over a period of 25 min and stirring continued overnight at room temperature. After quenching with NH$_4$Cl and concentration in vacuo the reaction mixture was taken up in NH$_4$Cl (500 mL) and extracted with MTBE (2 × 400 mL). The combined organic phases were washed with NH$_4$Cl (500 mL), H$_2$O (2 × 500 mL), saturated NaCl (500 L), dried (MgSO$_4$) and the solvent evaporated in vacuo. A solution of thus obtained crude 2-(pent-4-en-1-yn-1-yl)decahydro-naphthalen-2-ol (**27a**, 120 g, 0.55 mol) in 80% aqueous HCOOH (200 mL) was heated at 90° for 16 h, cooled down to rt, neutralised with saturated Na$_2$CO$_3$ and extracted with MTBE (2 × 400 mL). The combined organic phases were washed with NaHCO$_3$ (2 × 400 mL), H$_2$O (2 × 400 mL), dried (MgSO$_4$) and concentrated in vacuo. The residue was distilled using a Vigreux column (145–146 °C/0.1 torr) to give a mixture of five isomers (22 + 8 + 15 + 13 + 42%) of 1-(1, 4, 4a, 5, 6, 7, 8, 8a-octahydronaphthalen-2-yl)pent-4-ene-1-one and 1-(3, 4, 4a, 5, 6, 7, 8, 8a-octahydronaphthalen-2-yl)pent-4-ene-1-one (54.2 g, 44%). The main isomer, *cis*-1-(1,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)pent-4-ene-1-one (**7a**) was isolated by sequential preparative GLC using a multicapillary *MC-1* (Alltech) and a *DB*^{TM}-*5* column. ^{1}H NMR: δ 6.85 (m, 1H), 5.84 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.04 (dq, *J* = 17.1, 1.6, 1H), 4.97 (ddt, *J* = 10.2, 1.8, 1.2, 1H), 2.74 (m, 2H), 2.36 (m, 2H), 2.29 (m, 1H), 2.25–2.13 (m, 3H), 1.91–1.79 (m, 2H), 1.63–1.50 (m, 2H), 1.46–1.30 (m, 6H). ^{13}C NMR: δ 200.7 (s), 138.3 (d), 137.7 (d), 137.2 (s), 114.8 (t), 36.2 (t), 32.4 (d), 32.3 (d), 30.1 (t), 28.9 (t), 28.6 (t), 28.5 (t), 26.0 (t), 23.6 (t), 22.9 (t). MS: 218 (M$^+$, 8), 177(2), 163(100), 145(4), 135(11), 107(12), 93(24), 91(16), 79(21), 67(21), 55(20), 41(11). HRMS: calcd for $C_{15}H_{22}O$: 218.1671. Found: 218.1668. IR (isomer mixture): ν_{max} 2923vs, 2853s, 2704w, 1711w, 1668vs, 1640s, 1447m, 1185m, 910m.

The following **1-cycloalkenylpent-4-en-1-ones 28** were prepared according to this general procedure.

(±)-1-(5-*tert*-Butylcyclohex-1-enyl)pent-4-en-1-one (28a) and (±)1-(3-*tert*-Butylcyclohex-1-enyl)pent-4-en-1-one (28b). 7:3 mixture separated on *DB*^{TM}-*1* column. **28a** (2nd eluted): ^{1}H NMR δ 6.91 (m, 1H), 5.84 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.04 (dq, *J* = 17.1, 1.6, 1H), 4.97 (ddt, *J* = 10.2, 1.8, 1.3, 1H), 2.74 (m, 2H), 2.49 (m, 1H), 2.43–2.32 (m, 3H), 2.29–2.16 (m, 1H), 1.89–1.74 (m, 2H), 1.27–1.02 (m, 2H), 0.90 (s, 9H). ^{13}C NMR: δ 200.7 (s), 139.6 (s), 139.5 (d), 137.7 (d), 114.9 (t), 43.8 (d), 36.3 (t), 32.2 (s), 28.7 (t), 27.5 (t), 27.2 (3q), 24.8 (t), 23.0 (t). MS: 220 (M$^+$, 13), 205(6), 166(11), 165(100), 163(13), 109(15), 107(13), 95(18), 81(22), 79(11), 57(27), 55(14), 41(13). HRMS: calcd for $C_{15}H_{24}O$: 220.1827. Found: 220.1818. **28b** (1st eluted): ^{1}H NMR δ 6.90 (m, 1H), 5.85 (ddt, *J* = 17.1, 10.2, 6.6, 1H), 5.04 (dq, *J* = 17.1, 1.6, 1H), 4.97 (ddt, *J* = 10.2, 1.8, 1.3, 1H), 2.75 (m, 2H), 2.44–2.33 (m, 3H), 2.07 (m, 1H), 2.03–1.92 (m, 3H), 1.39 (m, 1H), 1.27–1.15 (m, 1H), 0.95 (s, 9H). ^{13}C NMR: δ 200.7 (s), 141.5 (d), 140.0 (s), 137.7 (d), 115.0 (t), 47.0 (d), 36.3 (t), 33.3 (s), 28.7 (t), 27.5 (3q), 23.6 (t), 23.3 (t), 22.2 (t). MS: 220 (M^+, 2), 205(2), 165(14), 164(100), 123(33), 108(49), 95(14), 79(13), 57(39), 41(15). HRMS: calcd for $C_{15}H_{24}O$: 220.1827. Found: 220.1842. IR (**28a + 28b**): IR: ν_{max} 2958vs, 2866s, 1670vs, 1642m, 1365m, 1240m, 1194m, 911m.

1-(4-*tert*-Butylcyclohex-1-enyl)pent-4-en-1-one (28c). ^{1}H NMR: δ 6.91 (m, 1H), 5.83 (ddt, J = 17.1, 10.3, 6.6, 1H), 5.03 (dq, J = 17.1, 1.7, 1H), 4.96 (ddt, J = 10.2, 1.8, 1.3, 1H), 2.73 (m, 2H), 2.55 (m, 1H), 2.40–2.24 (m, 3H), 2.09–1.87 (m, 3H), 1.32–1.22 (m, 1H), 1.08 (m, 1H), 0.89 (s, 9H). ^{13}C NMR: δ 200.0 (s), 139.9 (d), 138.9 (s), 137.5 (d), 114.7 (t), 43.3 (d), 36.1 (t), 31.9 (s), 28.4 (t), 27.6 (t), 26.9 (3q), 24.5 (t), 23.3 (t). MS: 220 (M^+, 8), 205(3), 192(3), 166(13), 165(100), 163(9), 149(4), 137(5), 123(6), 121(6), 109(9), 107(14), 95(20), 83(10), 81(30), 79(18), 77(12), 57(42), 55(22), 41(17). IR: ν_{max} 2960vs, 2869s, 1669vs, 1643s, 1365s, 1166m, 911m. Anal. calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.97; H, 10.80%.

1-Cyclooct-1-enylpent-4-en-1-one (28d). ^{1}H NMR: δ 6.88 (t, J = 8.3, 1H), 5.84 (ddt, J = 17.1, 10.2, 6.6, 1H), 5.03 (dq, J = 17.1, 1.7, 1H), 4.96 (ddt, J = 10.2, 1.9, 1.3, 1H), 2.76 (m, 2H), 2.45 (m, 2H), 2.35 (m, 4H), 1.63 (m, 2H), 1.56–1.38 (m, 6H). ^{13}C NMR: δ 200.0 (s), 142.4 (s), 142.0 (d), 137.4 (d), 114.7 (t), 36.0 (t), 29.0 (t), 28.9 (t), 28.7 (t), 27.3 (t), 26.4 (t), 25.9 (t), 23.4 (t). MS: 192 (M^+, 16), 177(3), 163(4), 151(4), 137(100), 135(6), 121(5), 109(24), 95(8), 91(9), 81(20), 79(17), 77(9), 67(79), 55(38), 53(14), 41(19). IR: ν_{max} 2925vs, 2852s, 1667vs, 1639s, 1465m, 1446m, 1090m, 908m. Anal. calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.17; H, 10.33%.

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References and Notes

1. For review cf. (a) Rossiter, K. *Chem. Rev.* **1996**, *96*, 3201. (b) Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633. (c) Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Fráter, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2980. (d) Boelens, M. *Perfumer Flavorist* **2002**, *27* (July/August), 34.
2. Firestein, S. *Nature* **2001**, *413*, 211.
3. Malnic, B.; Hirono, J. T.; Sato, T.; Buck, L. B. *Cell* **1999**, *96*, 713.
4. (a) Zozulya, S.; Echeverri, F.; Nguyen, T. *Genome Biol.* [online computer file] **2001**, *2*. URL:http://genomebiology.-com/2002/2/6/research/0018. (b) Mombaerts, P. *Annu. Rev. Genomics Hum. Genet.* **2001**, *2*, 493. (c) Glusman, G.; Yanai, I.; Rubin, I.; Lancet, D. *Genome Res.* **2001**, *11*, 685.
5. Called substantivity by perfumers and fragrance chemists.
6. Gimelbrant, A. A.; Haley, S. L.; McClintock, T. S. *J. Biol. Chem.* **2000**, *1*, 1.
7. An eminent exception is constituted by the I7 rat olfactory receptor (specific for C_{7-10} aliphatic aldehydes) assay, albeit it is far from being straightforward and its meaningfulness to humans has not been proven: Araneda, R. C.; Kini, A. D.; Firestein, S. *Nat. Neurosci.* **2000**, *3*, 1248.
8. These approaches, based on slight structural changes of a known lead ('me-too') or combining structural features of different molecules having similar pharmacologoical effects ('mecano') are probably still the most successful approaches in bringing new medicins to the market.
9. Bauer, K.; Garbe, D.; Surburg, H. *Common Fragrance and Flavor Materials*; Wiley-VCH: Weinheim (Ger.), 2001; p 196, and references cited therein.
10. (a) Teisseire, P.; Corbier, B.; Plattier, M. *Recherches (Paris)* **1967**, *16*, 5. (b) Näf, F.; Decorzant, R.; Thommen, W.; Willhalm, B.; Ohloff, G. *Helv. Chim. Acta* **1975**, *58*, 1016.
11. Berger, R. G.; Drawert, F.; Kollmannsberger, H.; Nitz, S. *J. Food Sci.* **1985**, *50*, 1655.
12. Müller, D. G.; Clayton, M. N.; Gassmann, G.; Boland, W.; Marner, F.-J.; Schotten, T.; Jaenicke, L. *Naturwissenschaften* **1985**, *72*, 97 and references therein.
13. (a) Morris, A. F.; Näf, F.; Snowden, R. L. *Perfumer Flavorist* **1991**, *16*, 33. (b) Schulte-Elte, K.-H.; Willhalm, B.; Gautschi, F. US Patent 4147672, 1979 (priority 1974, to Firmenich); *Chem. Abstr.* **1979**, *91*, 19986.
14. Arctander, S. *Perfume and Flavor Chemicals (Aroma Chemicals)*; Allured: Carol Stream, IL, USA, 1994; Vol. 1, No 77.
15. Bauer, K.; Garbe, D.; Surburg, H. *Common Fragrance and Flavor Materials*; Wiley-VCH: Weinheim (Ger.), 2001; p 23.
16. Sprecker, M., A. US Patent 4735932, 1988 (priority 1987, to IFF); *Chem. Abstr.* **1988**, *109*, 169913.
17. Bauer, K.; Garbe, D.; Surburg, H. *Common Fragrance and Flavor Materials*; Wiley-VCH: Weinheim (Ger.), 2001; p 93.
18. Bourdin, B.; Fráter, G.; Bajgrowicz, J. A. Eur. Pat. Appl. 913383, 1999 (priority 1997, to Givaudan); *Chem. Abstr.* **1999**, *130*, 338271.
19. Berg-Schultz, K.; Bajgrowicz, J. A. Eur. Pat. Appl. 1063229, 2000 (priority 1999, to Givaudan); *Chem. Abstr.* **2001**, *134*, 61263.
20. Goeke, A.; Berg-Schulz, K.; Bajgrowicz, J. A. Eur. Pat. Appl. 1182190, 2002 (priority 2000, to Givaudan); *Chem. Abstr.* **2002**, *136*, 199956.
21. (a) Sandermann, W.; Casten, R. *Parfuem. Kosmet.* **1973**, *54*, 335. (b) Kraft, P. *Synthesis* **1999**, 695.
22. The price criteria and practical aspects are much more constraining and taken into consideration from the very early stages of the fragrance and flavour research than in the pharmaceutical studies.
23. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
24. Neuner-Jehle, N.; Etzweiler, F. In *Perfumes: Art, Science and Technology*; Müller, P. M.; Lamparsky, D., Eds; Elsevier Applied Science: London, 1991; p 153.
25. Massó, T.; Portella, A.; Rus, E. *Perfumer Flavorist* **1990**, *15*, 39.
26. Arctander, S. *Perfume and Flavor Chemicals (Aroma Chemicals)*; Allured: Carol Stream, IL, USA, 1994; Vol. 1, No 91.
27. Sprecker, M., A.; Schreiber, W. L.; Belko, R. P. US Patent 4780564, 1988 (priority 1987, to IFF); *Chem. Abstr.* **1989**, *110*, 231174.
28. Bajgrowicz, J. A.; Fráter, G. *Enantiomer* **2000**, *5*, 225.
29. Bajgrowicz, J. A.; Frank, I.; Fráter, G.; Hennig, M. *Helv. Chim. Acta* **1998**, *81*, 1349.

30. Catalyst^{TM} 4.6; Accelrys Inc.: 9685 Scranton Road, San Diego, CA 92121, USA.

31. (a) Greene, J.; Kahn, S.; Savoj, H.; Sprague, P.; Teig, S. J. *Chem. Inf. Comput. Sci.* **1994**, *34*, 1297. (b) Smellie, A.; Teig, S. L.; Towbin, P. *J. Comp. Chem.* **1995**, *16*, 171. (c) Smellie, A.; Kahn, S. D.; Teig, S. L. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 285 and 295.

32. As it is difficult to find the consensus on the most appropriate ΔE, the values of 5, 10 and 15 kcal/mol were tried. The hypotheses generated using the last two values gave the highest and comparable correlation factor values.

33. Li, H.; Sutter, J.; Hoffmann, R. In *Pharmacophore Perception, Development and Use in Drug Design*; Guner, O. Ed.; IUL BioTechnology Series; International University Line; La Jolla, 2000; p 173.

34. The *correlation* factor could have been significantly higher if we had included more inactive molecules, structurally more different from the active ones. This would however not improve the quality of the generated hypotheses.

35. Generated using Moloc software: http://www.moloc.ch.

36. Other possibilities to discriminate between structurally similar active and inactive odorants by delimiting the hypothetical lipophilic part of the binding site consist in placing the Catalyst^{TM} *excluded volumes* and/or using the *shape* parameter. They are being tried.

37. Pellet, M.; Huet, F.; Conia, J.-M. *J. Chem. Res. Miniprint* **1982**, 2546.

38. Igarashi, M.; Tada, M. *Synthesis* **1996**, 465.

39. Garst, M. E.; Syage, E. T. Eur. Pat. Appl. 429287, 1991 (priority 1989, to Allergan); *Chem. Abstr.* **1991**, *115*, 183071.

40. Stetter, H.; Kuhlmann, H. *Synthesis* **1979**, 29.

41. Herz, W. *J. Org. Chem.* **1955**, *20*, 1062.

42. Hajek, M.; Malek, J. *Collect. Czech. Chem. Commun.* **1980**, *45*, 1940.

43. Marshall, J. A.; Andersen, N. H.; Hochstetler, A. R. *J. Org. Chem.* **1967**, *32*, 113.

44. Schulte-Elte, K.-H.; Mueller, B.; Pamingle, H. Eur. Pat. Appl. 155591, 1985 (priority 1984, to Firmenich); *Chem. Abstr.* **1986**, *105*, 191435.