

**(12) PATENT**  
**(19) AUSTRALIAN PATENT OFFICE**

**(11) Application No. AU 199869986 B2**  
**(10) Patent No. 726079**

(54) Title **Dioxacycloalkan-8-one**

(51)<sup>6</sup> International Patent Classification(s)  
**C07D 321/00 A61K 007/46**  
**A61K 007/00**

(21) Application No: **199869986** (22) Application Date: **1998.06.09**

(30) Priority Data

(31) Number **97109303** (32) Date **1997.06.09** (33) Country **CH**

(43) Publication Date : **1998.12.10**  
(43) Publication Journal Date : **1998.12.10**  
(44) Accepted Journal Date : **2000.11.02**

(71) Applicant(s)  
**Givaudan-Roure (International) SA**

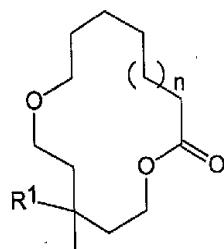
(72) Inventor(s)  
**Philip Kraft**

(74) Agent/Attorney  
**SPRUSON and FERGUSON, GPO Box 3898, SYDNEY NSW 2001**

## Dioxacycloalkan-8-one

### Abstract

The invention is concerned with 14- to 17-membered 4-methyl substituted 1,7-dioxacycloalkan-8-ones and 14- to 16-membered 1,7-dioxacycloalkan-8-ones with 4,4-dimethyl substitution, of the  
5 formula



wherein  $R^1 = H$  and  $n = 1-4$

or  $R^1 = CH_3$  and  $n = 1-3$

the use of these compounds as odorants as well as an economical process for their manufacture.

10

**AUSTRALIA**  
**PATENTS ACT 1990**

**COMPLETE SPECIFICATION**

**FOR A STANDARD PATENT**

**ORIGINAL**

---

Name and Address  
of Applicant: Givaudan-Roure (International) SA  
CH-1214 Vernier  
Geneve  
SWITZERLAND

Actual Inventor(s): Philip Kraft

Address for Service: Spruson & Ferguson, Patent Attorneys  
Level 33 St Martins Tower, 31 Market Street  
Sydney, New South Wales, 2000, Australia

Invention Title: Dioxacycloalkan-8-one

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

The invention is concerned with 14- to 17-membered 4-methyl substituted 1,7-dioxacycloalkan-8-ones and 14- to 16-membered 4,4-dimethyl substituted 5 1,7-dioxacycloalkan-8-ones, the use of these compounds as odorants and a cost-effective process for their manufacture.

*Warm, sweet-powdery bottom notes* with musk-like olfactory properties, which can extend from *flowery-sweet* (musk ambrette) via *powdery-animalic* (musk 10 ketone) to even *herby-woody* tonalites (musk xylene) are almost indispensable in the composition of a perfume as well in the perfuming e.g. of cosmetics, washing and cleaning agents, conditioners or air fresheners. Having regard to such olfactory characteristics and not least also because of their industrially simple and economical synthesis, aromatic musk substances have earned 15 particular significance in perfumery and have been used universally and in high dosages. These compounds, especially musk xylene and musk ambrette, have, however, a certain toxicity, especially phototoxicity, and poor biological degradability. Depending on territorial regulations they should or must no longer be used in new creations and should or must also be replaced by other 20 compounds in old creations.

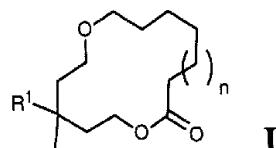
Other compounds with musk-like olfactory properties, especially toxicologically harmless macrocycles, are, however, significantly more expensive and have, *inter alia*, other side notes. Accordingly, when a nitromusk is replaced 25 by a macrocycle the overall olfactory impression of a composition usually changes substantially. Moreover, the macrocycles which are commercially available today are by far not as facet-rich as the series of aforementioned highly substituted aromatics.

30 From the foregoing it will be evident that there exists a great need for novel toxicologically harmless macrocyclic compounds with novel olfactory notes, especially such which are reminiscent of aromatic musk substances or with which similar facet-rich perfumistic effects can be produced. Moreover, such macrocyclic compounds should be simple and economical to manufacture in 35 order that they can be used not only in luxury perfumes, but also in products which are needed every day in the home, e.g. in cosmetics, washing and cleaning agents, conditioners or air fresheners.

0

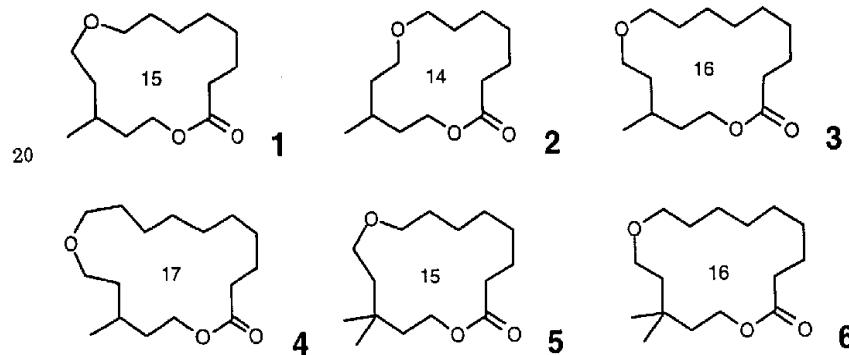
The object of the present is to satisfy this need and to provide such compounds. Moreover, these compounds should be cost-effective to manufacture.

The object is achieved by the 4-methyl substituted 1,7-dioxacycloalkan-8-one class of compound, which satisfies the requisite demands in an ideal manner. They are represented by general formula I



10                   wherein                    $R^1 = H$            and     $n = 1-4$   
                          or                            $R^1 = CH_3$            and     $n = 1-3$ .

The class of compound in accordance with the invention accordingly embraces the 14- to 17-membered 1,7-dioxacycloalkan-8-ones with methyl substitution in the 4-position and the 14- to 16-membered 1,7-dioxacycloalkan-8-ones with dimethyl substitution in the 4-position. The compounds with the following formulae 1-6 are examples of the novel class of compound, with the compounds having formulae 1, 3 and 4 being especially prominent organoleptically.



The compounds of general formula I have perfumistically interesting, *powdery-warm, for the most part musk-like olfactory notes with fresh-floral to herb-like accents* as well as a good adhesion and are biologically decomposable. They are capable, alone or in combination with other macrocyclic odorants, of replacing toxicologically questionable compounds with the same or similar

0 olfactory notes such as, for example, musk ambrette in the fields of use mentioned earlier. Further, having regard to their facet-rich olfactory properties, they give, not only individually but also in combination, interesting new effects in new compositions. The olfactory notes thereby extend from the 14- to the 17-membered compounds from *weakly musk-like, anise-like, herby, saffron, myrrh to strongly musk-like animalic*. In particular, compounds 1, 3 and 4 are especially striking in this respect.

The compounds of general formula I harmonize with a large number of natural and synthetic products which are frequently used in odorant compositions.

10 Especially in the chypre olfactory direction, for example in combination with a leathery accord, or in floral salicylate perfumes the compounds of general formula I give very interesting perfumistic effects. In particular, the compound 1 is ideally also suited for the composition of sweet fougère notes of the "Brut" (Fabergé, 1964) type and its more complex modern successors. The 15 use is, however, limited neither to this type of perfume nor to special olfactory directions, odorants or classes of substance. Examples of classes of substance which harmonize especially well are:

- ethereal oils and extracts: e.g. castoreum, costusroot oil, oak moss

20 absolute, geranium oil, jasmin absolute, patouli oil, rose oil, sandalwood oil or ylang-ylang oil;

- alcohols: e.g. citronellol, Ebanol®, eugenol, geraniol,

25 Javanol®, linalool, phenylethyl alcohol, Sandalore®, terpineol or Timberol®;

-aldehydes and ketones e.g. *alpha*-amylcinnamaldehyde,

30 Georgywood®, hydroxycitronellal, Iso-E-Super®, Isoraldein®, Hedion®, maltol, methylcedryl ketone, methylionone or vanillin;

- ethers and acetals: e. g. Ambrox®, geranyl methyl ether, rose

35 oxide or Spirambrene®;

0 - esters and lactones: e.g. benzyl acetate, cedryl acetate,  $\gamma$ -decalactone,  $\gamma$ -undecalactone or vetiveryl acetate;

5 - macrocycles: e.g. ambrettolide, Musk TM II® or Exaltolid®,

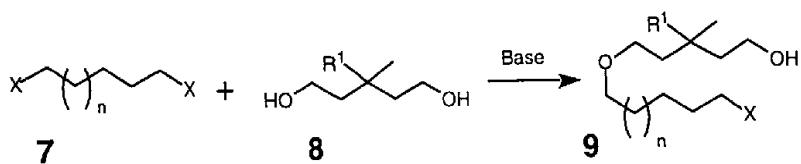
- heterocycles: e.g. isobutylquinoline.

10 The object of the cost-effective synthesis of the compounds of general formula I is achieved in accordance with the invention by a new access which starts from aliphatic dihalides and diols, which are readily accessible and economical starting materials. The synthesis sequence is based on a novel one-pot reaction comprising decarboxylation and cyclization which enables aliphatic hydroxymalonic esters to be cyclized directly to 14- to 17-membered

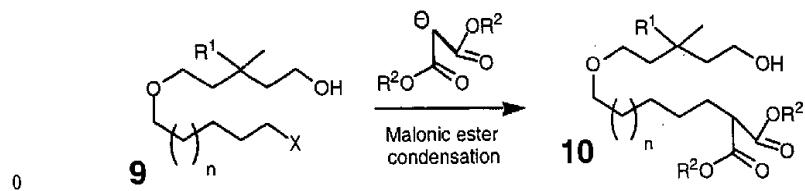
15 macrolides.

20 The novel synthesis sequence to 14- to 17-membered oxamacrolides, via which especially the compounds of general formula I are accessible economically, begins, as presented schematically hereinafter, with the Williamson reaction of an aliphatic dihalide 7 with  $n = 1-4$  and  $X = \text{Br or Cl}$  and a diol 8, whereby  $R^1 = \text{H or Me}$  for the synthesis of the compounds of general formula I, in the presence of a strong base, e.g. of sodium hydride. In addition to the dimeric condensation product 9 there are also obtained higher oligomers, which, however, do not interfere with the further reaction, and accordingly the

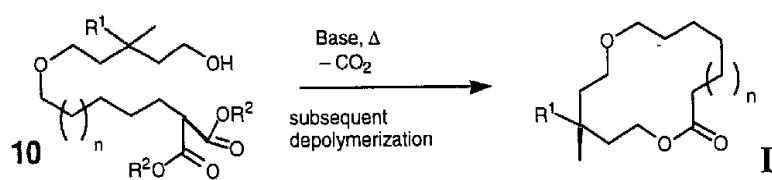
25 intermediate 9 need not be purified. Preferably, unused starting materials 7 and 8 are, after the reaction, separated by distillation for re-use.



30 The next step of the sequence is a malonic ester condensation which is carried out in a manner known per se and which from the haloalcohol 9 yields the hydroxymalonic ester 10 in which  $R^2 = \text{alkyl, preferably Me or Et.}$



In accordance with the invention the hydroxymalonic ester **10** is now without intermediary purification saponified in the novel one-pot reaction and polymerized with decarboxylation. The depolymerization and cyclization to 5 the target compound, especially to a compound of general formula I, is effected by a process known per se, e.g. according to the process described in U.S. Patent 2234551, which is presented schematically hereinafter.



10 By the one-pot decarboxylation-polymerization and by the described synthesis sequence the use of expensive long-chain aliphatic halocarboxylic acids, which represents the major cost factor in the conventional synthesis of 14- to 17-membered oxamacrolides, is circumvented.

15 Although the described synthesis sequence is preferably directed to the manufacture of compound of general formula I, it can also be used in accordance with the invention for the economical manufacture of already known 14- to 17-membered oxamacrolides.

20 The compounds in accordance with the invention, preferably the compounds 1 to 6, especially the compounds 1, 3 and 4, particularly the compound 1, can be used individually or in combination as odorants. Particularly interesting olfactory effects are produced in an odorant composition when the respective  
25 compound is replaced by a content of about 0.1 to about 25 wt.%, preferably from 10 to 15 wt.%.

Further advantages, characteristics and particulars for illustrating the invention appear from the following description of preferred working examples:

0

**Example 1: Manufacture of 12-methyl-9-oxa-14-tetradecanolide (1)**

118 g (1.0 mol) of 3-methyl-1,5-pentanediol and 317 g (1.3 mol) of 1,6-di-  
bromohexane in 2.5 l of dioxan were treated at room temperature with 28 g  
5 (1.1 mol) of 95 percent sodium hydride and subsequently heated under reflux  
for 24 h. After cooling the reaction mixture was treated with 400 ml of water,  
neutralized with saturated ammonium chloride solution and subsequently  
extracted three times with 1 l of *tert*-butyl methyl ether each time. The  
10 combined organic extracts were washed with saturated ammonium chloride  
solution, dried over magnesium sulphate and concentrated on a rotary  
evaporator. Starting material and byproducts were removed by distillation in  
a vacuum at 150°C bath temperature and 0.09 mbar. As the distillation  
residue there were obtained 183 g of 66 percent 12-bromo-3-methyl-6-  
oxadodecan-1-ol (43%), which is sufficiently pure for the further reactions.

15

A sample, purified by bulb tube distillation at 200°C/0.03 mbar, shows the  
following spectroscopic data:

20 IR (film):  $\nu = 1112 \text{ cm}^{-1}$  ( $\nu_{as}$  C—O—C),  $1060 \text{ cm}^{-1}$  ( $\nu_s$  C—O—C),  $3389 \text{ cm}^{-1}$  ( $\nu$  O—  
H),  $1459 \text{ cm}^{-1}$  ( $\delta$  C—H),  $1377 \text{ cm}^{-1}$  ( $\delta$  CH<sub>3</sub>). — <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 0.93$  (d,  $J = 6.8 \text{ Hz}$ , 3H, 3-Me),  $1.35$ — $1.49$  (m, 6H, 2-, 9-, 10-H<sub>2</sub>),  $1.55$ — $1.65$  (m, 4H, 4-, 8-H<sub>2</sub>),  
1.72 (oct,  $J = 6.8 \text{ Hz}$ , 1H, 3-H),  $1.89$  (quint,  $J = 6.8 \text{ Hz}$ , 2H, 11-H<sub>2</sub>),  $2.19$  (br s,  
1H, OH),  $3.39$ — $3.49$  (m, 6H, 5-, 7-, 12-H<sub>2</sub>),  $3.65$  (ddd,  $J = 10.4$ , 4.0 and 4.0 Hz,  
1H, 1-H<sub>b</sub>),  $3.71$  (ddd,  $J = 10.4$ , 3.7 and 3.7, 1H, 1-H<sub>a</sub>). — <sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta =$   
25  $19.86$  (q, 3-Me),  $25.30$  (t, C-9),  $26.76$  (d, C-3),  $27.89$  (t, C-10),  $29.42$  (t, C-8),  
 $32.63$  (t, C-12),  $33.84$  (t, C-11),  $36.43$  (t, C-4),  $39.69$  (t, C-2),  $60.73$  (t, C-1),  
 $68.96$  (t, C-5),  $70.72$  (t, C-7). — MS (EI): m/z (%) = 83 (100) [C<sub>6</sub>H<sub>11</sub>O<sup>⊕</sup>, 99 (61)  
[C<sub>6</sub>H<sub>11</sub>O<sup>⊕</sup>, 117 (7), [M<sup>⊕</sup>—C<sub>6</sub>H<sub>12</sub>Br], 163 / 165 (6) [M<sup>⊕</sup>—C<sub>6</sub>H<sub>13</sub>O<sub>2</sub>], 263 / 265  
(2) [M<sup>⊕</sup>—OH].

30

A solution of 30 g (520 mmol) of 95 percent sodium methylate in 220 ml of dry  
methanol was heated to reflux. Thereupon, 60 ml (520 mmol) of dimethyl  
malonate were allowed to drop in, the reaction mixture was heated under  
reflux for a further 15 min. and then 182 g of 66 percent 12-bromo-3-methyl-6-  
35 oxadodecan-1-ol from the preceding batch were added thereto. After heating  
under reflux for 14 hours the reaction mixture was added to 1.6 l of water/*tert*-  
butyl methyl ether (1:1) and made acid with concentrated phosphoric acid.  
The organic phase was separated and the aqueous phase was extracted twice

0 with 500 ml of *tert*-butyl methyl ether each time. The combined organic phases were dried over magnesium sulphate, concentrated to dryness on a rotary evaporator, taken up in 400 ml of methanol and treated with 99 g (1.5 mol) of 85 percent potassium hydroxide. Methanol and byproducts were distilled off at 180°C/20-23 mbar during 1 h. Thereupon, the reaction mixture was treated  
5 with 200 ml (2.4 mol) of 3-chloro-1,2-propanediol and heated to 140°C for 1 h. After distilling off the excess 3-chloro-1,2-propanediol the reaction vessel was fitted with a condenser and separator and treated with 6.0 g (86 mmol) of potassium methylate in 450 ml of anhydrous glycerol. After stirring at 140°C/20-30 mbar for 15 minutes the mixture was heated to reflux at 155°C/4-  
10 6 mbar for 3 days under the separator, with 6.0 g (86 mmol) of potassium methylate being added every 24 hours. The separated glycerol was poured into 800 ml of water and extracted three times with 500 ml of *tert*-butyl methyl ether each time. After drying the combined organic extracts over magnesium sulphate, concentration on a rotary evaporator and distillation at 95-  
15 97°C/0.04 mbar there were obtained 59 g (52%) of 12-methyl-9-oxa-14-tetradecanolide (1) as a colourless liquid with the following characteristics.

Odour: *Musk, flowery-woody, sweet-powdery, slightly anise-like, fresh, reminiscent of myrrh to musk ambrette, musk seed oil and tonkin musk.* - IR (film):  $\nu = 1735 \text{ cm}^{-1} (\text{v C=O})$ ,  $1116 / 1153 \text{ cm}^{-1} (\text{vas O-C-C})$ ,  $1247 \text{ cm}^{-1} (\text{vas C-C(=O)-O})$ ,  $1209 \text{ cm}^{-1} (\text{vas C-O-C})$ ,  $1352 \text{ cm}^{-1} (\delta \text{ CH}_3)$ ,  $1054 \text{ cm}^{-1} (\text{vas C-O-C})$ . -  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 0.94$  (d,  $J = 6.4 \text{ Hz}$ , 3H, 12-Me),  $1.27-1.76$  (m, 14H, 3-H<sub>2</sub>-7-H<sub>2</sub> and 11-,13-H<sub>2</sub>),  $1.89$  (oct,  $J = 6.7 \text{ Hz}$ , 1H, 12-H),  $2.34$  (t,  $J = 6.4 \text{ Hz}$ , 2H, 2-H<sub>2</sub>),  $3.37-3.52$  (m, 4H, 8-,10-H<sub>2</sub>),  $4.16$  (ddd,  $J = 11.2, 9.9$  and  $3.3 \text{ Hz}$ , 1H, 14-H<sub>b</sub>),  $4.19$  (ddd,  $J = 11.2, 5.4$  and  $5.2 \text{ Hz}$ , 1H, 14-H<sub>a</sub>). -  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 19.22$  (q, 12-Me),  $24.46$  (t, C-3),  $24.95$  (d, C-12),  $25.92$  (t, C-6),  $27.02 / 28.12 / 28.44$  (t, C-4,-5,-7),  $33.89$  (t, C-2),  $35.45 / 36.62$  (t, C-11,-13),  $61.51$  (t, C-14),  $67.60 / 69.61$  (t, C-8,-10),  $173.91$  (s, C-1). -  $^{\text{MS (EI)}}$ : m/z (%) = 55 (100) [ $\text{C}_4\text{H}_7^{\oplus}$ ], 83 (59) [ $\text{C}_6\text{H}_{11}^{\oplus}$ ], 99 (24) [ $\text{C}_6\text{H}_{11}\text{O}^{\oplus}$ ], 124 (31) [ $\text{M}^{\oplus}-\text{H}_2\text{O}-\text{C}_6\text{H}_{12}\text{O}$ ], 141 (19) [ $\text{M}^{\oplus}-\text{H}_2\text{O}-\text{C}_6\text{H}_{11}$ ], 213 (1) [ $\text{M}^{\oplus}-\text{CHO}$ ], 242 (1) [ $\text{M}^{\oplus}$ ]. -  $\text{C}_{14}\text{H}_{26}\text{O}_3$  (242.36): calculated C 69.38, H 10.81; found C 69.24, H 10.68.

The following compounds have been manufactured in an analogous manner using dihalides **6** of different length. For them there are therefore set forth  
35 only the spectroscopic data, the olfactory characteristics and the elementary analyses:

0

**Example 2: 11-Methyl-8-oxa-13-tridecanolide (2)**

Odour: *Saffron, anise-like, woody-flowery, piny-terpene like, fresh, slightly musk-like.* – IR (film):  $\nu = 1734 \text{ cm}^{-1}$  (v C=O), 1123 / 1155  $\text{cm}^{-1}$  (v<sub>as</sub> O–C–C), 1254  $\text{cm}^{-1}$  (v<sub>as</sub> C–C(=O)–O), 1203  $\text{cm}^{-1}$  (v<sub>as</sub> C–O–C), 1357  $\text{cm}^{-1}$  ( $\delta$  CH<sub>3</sub>), 1056 5  $\text{cm}^{-1}$  (v<sub>as</sub> C–O–C). – <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 0.96$  (d,  $J = 6.8 \text{ Hz}$ , 3H, 11-Me), 1.15 (dddd,  $J = 14.5, 10.0, 4.8$  and 2.4 Hz, 1H, 12-H<sub>b</sub>), 1.25–1.79 (m, 10H, 3-H<sub>2</sub>–6-H<sub>2</sub>, 10-H<sub>2</sub>), 1.85 (dddd,  $J = 14.5, 7.6, 7.3$  and 3.9 Hz, 1H, 12-H<sub>a</sub>), 1.99 (m<sub>c</sub>, 1H, 11-H), 2.31 (ddd,  $J = 14.8, 8.3$  and 3.7 Hz, 1H, 2-H<sub>b</sub>), 2.41 (ddd,  $J = 14.8, 9.3$  and 3.7 Hz, 1H, 2-H<sub>a</sub>), 3.33–3.50 (m, 4H, 7–9-H<sub>2</sub>), 3.98 (ddd,  $J = 11.2, 11.0$  and 2.4 Hz, 1H, 13-H<sub>b</sub>), 4.53 (ddd,  $J = 11.2, 4.6$  and 3.6 Hz, 1H, 13-H<sub>a</sub>). – <sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta = 19.47$  (q, 11-Me), 23.72 (d, C-11), 25.32 / 25.51 / 26.81 (t, C-3–C-5), 28.62 (t, C-6), 33.79 (t, C-2), 34.53 (t, C-12), 36.51 (t, C-10), 60.96 (t, C-13), 66.91 / 68.85 (t, C-7, -9), 173.78 (s, C-1). – MS (EI): m/z (%) = 55 (100) [C<sub>4</sub>H<sub>7</sub><sup>⊕</sup>], 83 (79) [C<sub>6</sub>H<sub>11</sub><sup>⊕</sup>], 101 (48) [C<sub>6</sub>H<sub>13</sub>O<sup>⊕</sup>], 111 (24) [C<sub>6</sub>H<sub>13</sub>O<sup>2+</sup>], 127 (30) 10 [M<sup>⊕</sup>–C<sub>6</sub>H<sub>13</sub>O], 145 (4) [M<sup>⊕</sup>–C<sub>6</sub>H<sub>11</sub>], 169 (2) [M<sup>⊕</sup>–C<sub>2</sub>H<sub>3</sub>O<sub>2</sub>], 199 (1) [M<sup>⊕</sup>–CHO], 228 (1) [M<sup>⊕</sup>]. – C<sub>13</sub>H<sub>24</sub>O<sub>3</sub> (228.33): calculated C 68.38, H 10.60; found C 68.55, H 10.57.

20

**Example 3: 13-Methyl-10-oxa-15-pentadecanolide (3)**

Odour: *Musk, animalic, warm-powdery, flowery, slightly after saffron.* – IR (film):  $\nu = 1734 \text{ cm}^{-1}$  (v C=O), 1118 / 1151  $\text{cm}^{-1}$  (v<sub>as</sub> O–C–C), 1250  $\text{cm}^{-1}$  (v<sub>as</sub> C–C(=O)–O), 1357  $\text{cm}^{-1}$  ( $\delta$  CH<sub>3</sub>), 1061  $\text{cm}^{-1}$  (v<sub>as</sub> C–O–C). – <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 0.91$  (d,  $J = 6.4 \text{ Hz}$ , 3H, 13-Me), 1.31–1.66 (m, 15H, 3-H<sub>2</sub>–8-H<sub>2</sub>, 12-H<sub>2</sub>, 14-H<sub>b</sub>), 1.83 (ddt,  $J = 19.1, 9.6$  and 5.0 Hz, 1H, 14-H<sub>a</sub>), 1.93 (m<sub>c</sub>, 1H, 13-H), 2.33 (dd,  $J = 6.9$  and 6.2 Hz, 2H, 2-H<sub>2</sub>), 3.34–3.52 (m, 4H, 9–11-H<sub>2</sub>), 4.14 (ddd,  $J = 11.0, 5.5$  and 5.0 Hz, 1H, 15-H<sub>b</sub>), 4.21 (ddd,  $J = 11.0, 10.0$  and 4.0 Hz, 1H, 15-H<sub>a</sub>). – <sup>13</sup>C-NMR (CDCl<sub>3</sub>):  $\delta = 18.22$  (q, 13-Me), 24.67 / 25.26 (t, C-3, -7), 25.53 (d, C-13), 27.21 / 27.40 / 27.52 (t, C-4, -5, -6), 28.68 (t, C-8), 34.67 (t, C-2), 35.49 (t, C-14), 37.01 (t, C-12), 61.74 (t, C-15), 67.67 / 70.16 (t, C-9, -11), 173.93 (s, C-1). – MS (EI): m/z (%) = 55 (100) [C<sub>4</sub>H<sub>7</sub><sup>⊕</sup>], 83 (64) [C<sub>6</sub>H<sub>11</sub><sup>⊕</sup>], 99 (30) [C<sub>6</sub>H<sub>11</sub>O<sup>⊕</sup>], 138 (25) [M<sup>⊕</sup>–C<sub>6</sub>H<sub>14</sub>O<sub>2</sub>], 155 (23) [M<sup>⊕</sup>–C<sub>6</sub>H<sub>13</sub>O], 213 (2) [M<sup>⊕</sup>–C<sub>2</sub>H<sub>3</sub>O], 227 (2) [M<sup>⊕</sup>–CHO], 256 (1) [M<sup>⊕</sup>]. – C<sub>15</sub>H<sub>28</sub>O<sub>3</sub> (256.39): calculated C 70.27, H 11.01; found C 70.26, H 11.09.

35

0                   **Example 4: 14-Methyl-11-oxa-16-hexadecanolide (4)**

Odour: *Animalic, must, sweet, erogenous, warm-powdery.* – IR (film):  $\nu = 1735\text{ cm}^{-1}$  ( $\nu\text{ C=O}$ ),  $1117 / 1151\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ O-C-C}$ ),  $1254\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ C-C(=O)-O}$ ),  $1361\text{ cm}^{-1}$  ( $\delta\text{ CH}_3$ ),  $1060\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ C-O-C}$ ). –  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 0.92$  (d,  $J = 6.8\text{ Hz}$ , 3H, 14-Me),  $1.29 - 1.56$  (m, 14H, 4-H<sub>2</sub>–9-H<sub>2</sub>, 13-H<sub>2</sub>),  $1.61 - 1.67$  (m, 3H, 3-H<sub>2</sub>, 15-H<sub>b</sub>),  $1.79$  (ddt, 14.0, 8.4 and 5.2 Hz, 1H, 15-H<sub>a</sub>),  $1.87$  (m<sub>c</sub>, 1H, 14-H),  $2.33$  (dd,  $J = 6.8$  and 6.0 Hz, 2H, 2-H),  $3.84 - 3.50$  (m, 4H, 10-,12-H<sub>2</sub>),  $4.15$  (ddd,  $J = 11.2$ , 6.0 and 5.2 Hz, 1H, 16-H<sub>b</sub>),  $4.18$  (ddd,  $J = 11.2$ , 8.4 and 4.4 Hz, 1H, 16-H<sub>a</sub>). –  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 18.54$  (q, 14-Me),  $24.80 / 26.15$  (t, C-3,-8),  $26.17$  (d, C-14),  $27.31 / 27.66 / 27.79 / 28.22$  (t, C-4–C-7),  $29.15$  (t, C-9),  $34.02$  (t, C-2),  $35.57$  (t, C-15),  $37.00$  (t, C-13),  $62.14$  (t, C-16),  $68.05 / 70.77$  (t, C-10,-12),  $174.14$  (s, C-1). – MS (EI): m/z (%) = 55 (100) [ $\text{C}_4\text{H}_7^{\oplus}$ ], 83 (71) [ $\text{C}_6\text{H}_{11}^{\oplus}$ ], 99 (33) [ $\text{C}_6\text{H}_{11}\text{O}^{\oplus}$ ], 113 (13) [ $\text{M}^{\oplus}\text{--C}_{10}\text{H}_{21}\text{O}$ ], 153 (15) [ $\text{M}^{\oplus}\text{--C}_6\text{H}_{13}\text{O}_2$ ], 169 (16) [ $\text{M}^{\oplus}\text{--C}_6\text{H}_{13}\text{O}$ ], 171 (9) [ $\text{C}_{10}\text{H}_{19}\text{O}_2^{\oplus}$ ], 227 (1) [ $\text{M}^{\oplus}\text{--C}_2\text{H}_3\text{O}$ ], 241 (2) [ $\text{M}^{\oplus}\text{--CHO}$ ], 270 (1) [ $\text{M}^{\oplus}$ ]. –  $\text{C}_{16}\text{H}_{30}\text{O}_3$  (270.41): calculated C 71.07, H 11.18; found C 71.37, H 11.13.

•••••           **Example 5: 12,12-Dimethyl-9-oxa-14-tetradecanolide (5)**

20                   Odour: *Relatively weak, powdery musk-like, woody-herby.* – IR (film):  $\nu = 1734\text{ cm}^{-1}$  ( $\nu\text{ C=O}$ ),  $1117 / 1154\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ O-C-C}$ ),  $1252\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ C-C(=O)-O}$ ),  $1366\text{ cm}^{-1}$  ( $\delta\text{ CH}_3$ ),  $1046\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ C-O-C}$ ). –  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 0.94$  (s, 6H, 12-Me<sub>2</sub>),  $1.31 - 1.42$  (m, 6H, 4-H<sub>2</sub>–6-H<sub>2</sub>),  $1.50 - 1.57$  (m, 4H, 3-,7-H<sub>2</sub>),  $1.69$  (t,  $J = 7.2\text{ Hz}$ , 2H, 11-H<sub>2</sub>),  $1.71$  (dd,  $J = 10.0$  and  $6.8\text{ Hz}$ , 2H, 13-H<sub>2</sub>),  $2.30$  (t,  $J = 6.6\text{ Hz}$ , 2-H<sub>2</sub>),  $3.39$  (t,  $J = 5.2\text{ Hz}$ , 8-H<sub>2</sub>),  $3.46$  (t,  $J = 6.2\text{ Hz}$ , 10-H<sub>2</sub>),  $4.16$  (t,  $J = 7.0\text{ Hz}$ , 2H, 14-H<sub>2</sub>). –  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 23.72$ ,  $24.91$  (t, C-3,-6),  $26.41 / 27.89$  (t, C-4,-5),  $28.59$  (2q, 12-Me<sub>2</sub>),  $29.05$  (t, C-7),  $31.77$  (s, C-12),  $34.59$  (t, C-2),  $38.86 / 40.57$  (t, C-11,-13),  $61.93$  (t, C-14),  $67.66 / 69.88$  (t, C-8,-10),  $174.15$  (s, C-1). – MS (EI): m/z (%) = 55 (100) [ $\text{C}_4\text{H}_7^{\oplus}$ ], 69 (72) [ $\text{C}_5\text{H}_9^{\oplus}$ ], 81 (40) [ $\text{C}_6\text{H}_9^{\oplus}$ ], 97 (59) [ $\text{C}_6\text{H}_9\text{O}^{\oplus}$ ], 113 (27) [ $\text{C}_7\text{H}_{13}^{\oplus}$ ], 125 (27) [ $\text{C}_8\text{H}_{13}\text{O}^{\oplus}$ ], 141 (15) [ $\text{M}^{\oplus}\text{--C}_6\text{H}_9\text{O--H}_2\text{O}$ ], 183 (2) [ $\text{M}^{\oplus}\text{--C}_4\text{H}_7\text{--H}_2\text{O}$ ], 227 (1) [ $\text{M}^{\oplus}\text{--CHO}$ ], 256 (1) [ $\text{M}^{\oplus}$ ]. –  $\text{C}_{15}\text{H}_{28}\text{O}_3$  (256.39): calculated C 70.27, H 11.01; found C 70.15, H 10.87.

35                   **Example 6: 13,13-Dimethyl-10-oxa-15-pentadecanolide (6)**

Odour: *relatively weak, fruity-musk like, reminiscent of ambrettone.* – IR (film):  $\nu = 1734\text{ cm}^{-1}$  ( $\nu\text{ C=O}$ ),  $1118 / 1150\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ O-C-C}$ ),  $1242\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ C-C(=O)-O}$ ),  $1365\text{ cm}^{-1}$  (d  $\text{CH}_3$ ),  $1055\text{ cm}^{-1}$  ( $\nu_{\text{as}}\text{ C-O-C}$ ). –  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta =$

0 0.95 (s, 6H, 13-Me<sub>2</sub>), 1.33–1.40 (m, 8H, 4-H<sub>2</sub>–7-H<sub>2</sub>), 1.49–1.55 (m, 4H, 8-,12-H<sub>2</sub>), 1.62 (m, 2H, 3-H<sub>2</sub>), 1.76 (t, *J* = 8.0 Hz, 2H, 14-H<sub>2</sub>), 2.32 (t, *J* = 6.4 Hz, 2H, 2-H<sub>2</sub>), 3.38 (t, *J* = 5.2 Hz, 2H, 11-H<sub>2</sub>), 3.47 (t, *J* = 5.8 Hz, 2H, 9-H<sub>2</sub>), 4.16 (t, *J* = 8.0 Hz, 2H, 15-H<sub>2</sub>). – <sup>13</sup>C-NMR (CDCl<sub>3</sub>): δ = 23.94 / 24.56 (t, C-3,-7), 25.84 / 26.36 / 26.52 (t, C-4,-5,-6), 28.04 (2q, 13-Me<sub>2</sub>), 29.23 (t, C-8), 31.79 (s, C-13), 34.53 (t, C-2), 39.02 (t, C-14), 41.28 (t, C-12), 61.98 (t, C-15), 67.82 / 70.49 (t, C-9,-11), 173.83 (s, C-1). – MS (EI): m/z (%) = 55 (100) [C<sub>4</sub>H<sub>7</sub><sup>⊕</sup>], 69 (92) [C<sub>5</sub>H<sub>9</sub><sup>⊕</sup>], 113 (39) [C<sub>8</sub>H<sub>17</sub><sup>⊕</sup>], 139 (29) [M<sup>⊕</sup>–C<sub>7</sub>H<sub>15</sub>O<sub>2</sub>], 155 (18) [M<sup>⊕</sup>–C<sub>7</sub>H<sub>15</sub>O], 197 (3) [M<sup>⊕</sup>–CO–C<sub>2</sub>H<sub>4</sub>O], 241 (2) [M<sup>⊕</sup>–CO], 270 (1) [M<sup>⊕</sup>]. – C<sub>16</sub>H<sub>30</sub>O<sub>3</sub> (270.41): calculated C 71.07, H 11.18; found C 70.89, H 11.11.

10

**Example 7:**

A masculine perfume composition "Oriental Fougere" was produced. The components are listed below. For this, 15 wt.% of compound 1 were used in place of the musk ambrette which is usual for this type of perfume composition. The composition contains no polycyclic musk odorants.

Compound 1 confers to the perfume a musk note, introduces sweetish-powdery effects reminiscent of nitromusk and therefore becomes more than a substitute for nitromusk. Its powderiness together with the tonkin musk aspect underlines the warm-powdery olfactory impression and contributes to the rounding-off of the top note and of the total composition.

	25	Composition:	
		Ingredients	Weight %
		1. Aldehyde C11 (10-undecen-1-al)	0.05
		2. Aldehyde C12 (lauric)	0.05
		3. $\alpha$ -Amyl cinnamic aldehyde	1.0
		4. Isoamyl salicylate	60.0
	30	5. Anisic aldehyde	30.0
		6. Benzyl acetate extra	20.0
		7. Benzyl salicylate	80.0
		8. Bergamot oil Italian	100.0
		9. Citronellyl formate	5.0
	35	10. Civet oil	1.0
		11. Coumarin pure crystalline	7.0
		12. Diethyl phthalate	1.8
		13. Dipropylene glycol	129.9

0	14. Geraniol extra	3.0
	15. Geranium oil African	70.0
	16. Heliotropin crystalline	30.0
	17. Hydroxycitronellal	90.0
	18. Lavender oil	50.0
5	19. Lemon oil Italian	50.0
	20. Lemongrass oil rectified	5.0
	21. Linalool synthetic	5.0
	22. Linalyl acetate synthetic	5.0
	23. Methyl anthranilate extra	3.0
10	24. Methyl $\beta$ -naphthyl ketone	3.0
	25. $\gamma$ -Undecalactone	0.1
	26. Petitgrain oil Paraguay pure	20.0
	27. Phenyl acetaldehyde 85%/PEA	0.1
	28. Phenyl ethyl alcohol white	15.0
15	29. Sandalwood oil East Indian	20.0
	30. Tarragon oil	25.0
	31. Terpineol pure	3.0
	32. Vanillin	7.0
	33. Vetiver oil (Bourbon)	10.0
20	34. Compound 1	<u>150.0</u>
		1000.0

**Example 8:**

25 A masculine perfume composition "Fresh Musk" was produced. 10 wt.% of compound 1 were used in analogy to Example 7. The components are listed below.

30 Compound 1 intensifies the musk character and adds a note reminiscent of nitromusk. The additional myrrh-jasmone aspect moderates the herb-spicy top note and thereby gives it completely new facets. Thus, compound 1 harmonizes very well and synergistically with other macrocyclic musk odorants, e.g. especially with cyclopentadecanolide, and can combine well with flowery notes such as e.g. jasmin.

Composition:		
	Ingredients	Weight %
0	1. Agrudor BAV 645/3	15.0
5	2. Ambretone (Musk TM II)	4.0
	3. Benzyl acetate extra	5.0
10	4. Benzyl salicylate	120.0
	5. Cepionate (Hedione)	5.0
	6. Dipropylene glycol	480.0
	7. Ethylene brassylate	200.0
	8. Hexyl cinnamic aldehyde	25.0
	9. Lavandin oil (Grosso)	5.0
	10. Lemon oil Italian	5.0
	11. Linalyl acetate synthetic	25.0
	12. Cyclopentadecanolide	10.0
	13. Tonka bean resinoid N.1 30%/DPG	1.0
15	14. Compound 1	<u>100.0</u>
		1000.0

**Example 9:**

20 A perfume oil with a modern lavender note, rounded off by fine flowery musk-like woody tones, for use in soaps was produced; it contained 10 wt.% of compound 1 in place of nitromusk otherwise usually used for this olfactory type.

25 The components of the composition are listed hereinafter.

The composition confers to the soap a very warm-powdery, pleasant effect, which, when the soap is used, underlines the cleansing and caring character.

0	Composition:	
	Ingredients	Weight %
	1. Acetaldehyde phenethylpropyl acetal	
	10% DPG	25.0
5	2. Allyl phenoxy acetate	5.0
	3. Aldehyde C10 (n-decanal)	6.0
	4. Aldehyde C11 (10-undecenal) 10% DPG	10.0
	5. Aldehyde C12 (lauric)	10.0
	6. Aldehyde C12 NMA 10 % DPG	32.0
10	7. Allyl amyl glycolate	8.0
	8. Allyl caproate	3.0
	9. Bergamyl acetate	25.0
	10. Cinnamic aldehyde	2.0
	11. Citronellal	5.0
15	12. Citronellol 750	30.0
	13. Coumarin pure crystalline	5.0
	14. Cyclamen aldehyde extra	5.0
	15. Dihydromyrcenol	110.0
	16. Ethyl vanillin 10% DPG	5.0
20	17. Eucalyptol	5.0
	18. Eugenol pure	5.0
	19. 3,6-Dimethyl- $\beta$ -resocin acid methyl ester	2.0
	20. Florhydral	5.0
	21. Fructone	5.0
25	22. Galbanum oil 10% DPG	15.0
	23. Geranitriol T	15.0
	24. Geranium oil African	15.0
	25. $\alpha$ -Hexyl cinnamic aldehyde	70.0
	26. 2,4,6-Trimethyl-3-cyclohexene-1-carboxaldehyde	9.0
30	27. Lavender oil (Grosso)	15.0
	28. Lilial	120.0
	29. Lime oxide	10.0
	30. Linalool synthetic	20.0
35	31. Menthanyl acetate	25.0
	32. Menthyl acetate	15.0
	33. <i>para</i> - <i>tert</i> -Butylcyclohexyl acetate	60.0
	34. Patchouli oil	18.0

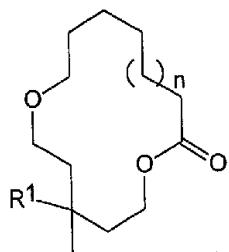
0	35. Phenyl ethyl acetate	10.0
	36. Phenyl ethyl alcohol white	30.0
	37. Rose oxide CO 10% DPG	5.0
	38. Rosemary oil	5.0
	39. Spearmint oil FCC NF extra	
5	KPF 10% DPG	10.0
	40. Terpineol pure	50.0
	41. Terpinyl acetate	15.0
	42. Tricyclal 10% DPG	10.0
	43. Tridecenonitrile 10% DPG	10.0
10	44. Verdol 10% DPG	15.0
	45. <i>ortho-tert</i> -Butylcyclohexyl acetate	10.0
	46. 1-Methyl-4-(4-methyl-3-pentenyl)-3-cyclohexene-1-carboxaldehyde	15.0
	47. Compound 1	<u>100.0</u>
15		1000.0

Analogous compositions to the compositions described in Examples 7 to 9 were also produced with compounds 3 and 4.

From all of these exemplified compositions it will be evident that the class of compound in accordance with the invention, especially at least of one of compounds 1, 3 and 4, preferably compound 1, is outstandingly suitable for use as odorants.

The claims defining the invention are as follows:

1. Compounds of general formula I



wherein R<sup>1</sup> = H and n = 1-4

5 or R<sup>1</sup> = CH<sub>3</sub> and n = 1-3

2. 12-Methyl-9-oxa-14-tetradecanolide (1).

3. 11-Methyl-8-oxa-13-tridecanolide (2).

4. 13-Methyl-10-oxa-15-pentadecanolide (3).

5. 14-Methyl-11-oxa-16-hexadecanolide (4).

10 6. 12,12-Dimethyl-9-oxa-14-tetradecanolide (5).

7. 13,13-Dimethyl-10-oxa-15-pentadecanolide (6).

8. A 2,8-dioxacyclo(tetra, penta, hepta or hepta) decan-1-one derivative, substantially as hereinbefore described with reference to any one of the Examples.

9. The use of at least one of the compounds in accordance with any one of claims 1 to 8 as

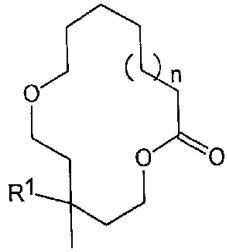
15 an odorant.

10. The use of at least one of the compounds in accordance with any one of claims 2 to 7 as an odorant.

11. The use of at least one of the compounds in accordance with any one of claims 2, 4 or 5 as an odorant.

20 12. The use according to claim 11, wherein the compound is 12-methyl-9-oxa-14-tetradecanolide (1).

13. An odorant composition containing a carrier and at least one of the compounds of formula I



wherein  $R^1 = H$  and  $n = 1-4$   
 or  $R^1 = CH_3$  and  $n = 1-3$ ,

14. The composition of claim 13 which contains at least one of the compounds in accordance with any one of claims 2 to 7.

15. The composition of claim 14 which contains at least one of the compounds in accordance with any one of claims 2, 4 or 5.

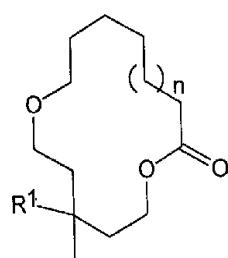
16. An odorant composition according to claim 15 containing the compound 12-methyl-9-oxa-14-tetradecanolide (1).

17. An odorant composition according to any one of claims 13 to 16, wherein the compounds are present therein to about 0.1 to about 25%.

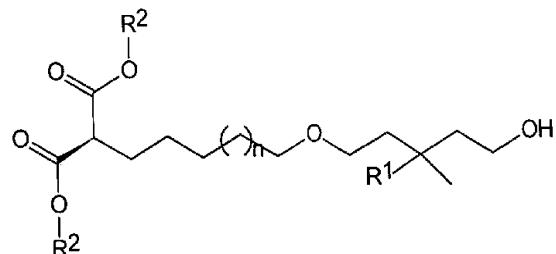
18. An odorant composition according to claim 17 wherein the compounds are present therein to 10 to 15%.

19. An odorant composition, substantially as hereinbefore described with reference to any one of the Examples.

15 20. A process for the manufacture of a compound of general formula I



wherein  $R^1 = H$  and  $n = 1-4$   
 or  $R^1 = CH_3$  and  $n = 1-3$ ,  
 which process comprises polymerising the hydroxymalonic ester 10.



20 10  
 wherein  $n = 1-4$  and  $R^2 = \text{alkyl}$ .

21. A process according to claim 20 wherein  $R^2$  is methyl or ethyl.

22. A process according to claim 20 or claim 21, wherein the polymerisation is effected with decarboxylation.

23. A process for the manufacture of a 2,8-dioxacyclo(tetra, penta, hepta or hepta) decan-1-one derivative, substantially as hereinbefore described with reference to any one of the Examples.

**Dated 5 June, 1998**  
**Givaudan-Roure (International) SA**

5

**Patent Attorneys for the Applicant/Nominated Person**  
**SPRUSON & FERGUSON**

33  
33  
33  
33  
33  
33  
33  
33