167. Synthesis of Enantiomeric 3-Oxa-analogues of *cis*-Rose Oxide and of Some Sesquiterpenoid Homologues

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Summary

The synthesis, spectral properties and sensory evaluation of chiral oxa-analogues of *cis*-rose oxide, and of eight corresponding sesquiterpenoid homologues, are described.

A suitable approach to the study of structure-activity relationships in connection with olfaction and other sensory properties (as affecting both humans and animals) is by way of structural modification of known substances of proved effectiveness. Such studies can lead to the design of model systems which serve as a guide for the synthesis of new compounds with possibly novel olfactory properties.

Past experience can point to a number of fragrances whose olfactory properties were not changed to any marked extent by modifying their molecular structure, *e.g.* such as by replacement of a methylene group by an O-atom. This is exemplified by the relationship of the ketone *Exaltone*® to the lactone *Exaltolide*®, and of similar oxa-ketones to the corresponding oxa-lactones [1] [2]. Three of the latter, 10-, 11-, and 12-oxahexadecanolides have been introduced to perfumery under the trade names *Musk* 906, *Musk* R-1 and *Cervolide*, respectively [3]. The olfactory similarity between *Furaneol*® or maltol and their carbocyclic analogues [4] [5] is as evident as between benzyl acetone and benzyl acetate [4].

In the wider context of sensory properties one can mention similar ant alarm pheromone activity among the pairs heptan-2-one/butyl acetate, and octan-2-one/2-ethoxyethyl acetate [6]. The activity of the *Cecropia* juvenile hormone is not only mimicked but even surpassed by certain of its 4-oxa-analogues with a farnesane molecular skeleton [7].

Moreover, similar phenomena have been observed among pharmacologically active compounds. To cite one example: certain 5-oxa- and 7-oxa-prostaglandin analogues were found to have prostaglandin-like activity, others proved to be prostaglandin antagonists, while a third group combined both properties [8] [9].

This paper describes our work on optically active 3-oxa-analogues of rose oxide (**3** and **4**) and their isoprenoid homologues **5** to **12**.

A number of preparative routes, albeit laborious and costly [10], have previously been described for the monoterpenoid tetrahydropyran [11] [12] whose (−)-*cis* isomer **1** is highly prized as a perfume constituent in view of its special olfactory properties [13]. An oxa-analogue of this compound seemed attractive to us as a less expensive substitute. Such an analogue could be obtained in its racemic form (**3**+**4**) in 80% yield by reaction of (±)-butane-1,3-diol with β-methylcrotonalde-

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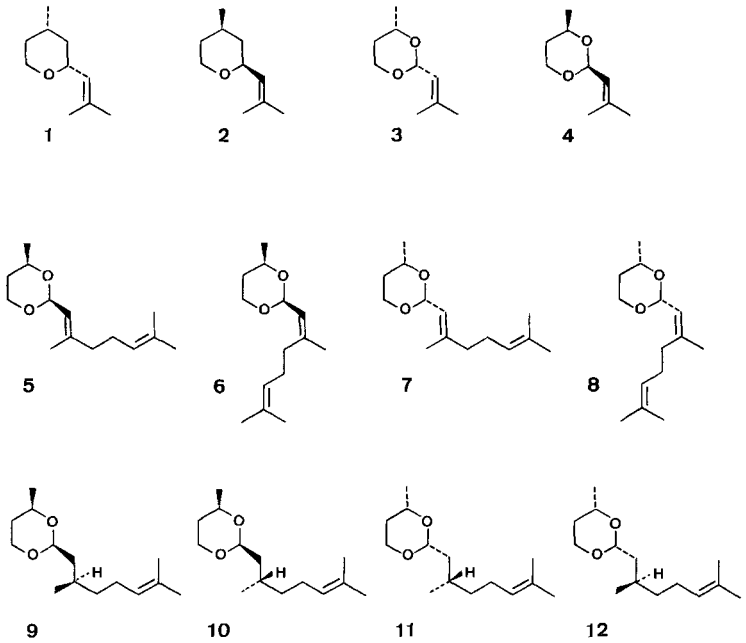

hyde (3-methylbut-2-enal) in the presence of *p*-toluenesulfonic acid [14]; the same route has been employed by *Hoffmann et al.* [15]. The product was almost exclusively the *cis*-isomer, only 1.2% being *trans*. In order to facilitate systematic comparison with rose oxide itself it was necessary to prepare enantiomers **3** and **4** separately, using optically active butane-1,3-diol which was obtained by resolution of the racemate with camphanoyl chloride [16]. The reaction conditions described above (catalysis by *p*-toluenesulfonic acid) led to partial racemization of the product. This could be avoided by using the milder acetalisation method described by *Johnson et al.* [17], and both enantiomeric *cis*-oxa-rose oxides **3** and **4** were obtained in a state of high optical purity.

Turning now to the preparation of sesquiterpenoid homologues of these compounds we subjected citral and both enantiomers of citronellal to acetalization in the same manner, to give the diastereoisomeric *cis*-acetals **5** to **12** in up to 90% yield. In compounds **5** to **8** the configuration of the double bond follows from the composition of the starting citral (geranial/neral 65:35). (+)-Citronellal gave the optically active acetals **9** and **12**, while **10** and **11** resulted from the (−)-enantiomer. The structure assignment and configuration of these compounds are evident from their spectroscopic data (see Experimental Part).

Sensory evaluation. – Olfactory examination of the oxa-rose oxides **3** and **4** [14] reveals a remarkably analogous relationship to the *cis*-rose oxide enantiomers **1** and **2** [12]. The odour of acetals **3** and **4** has a basic geranium-type note; that of **3** is more floral and less herbal and with a myrrh and saffron supplement, while **4** shows a deeper base note with a green and camphoraceous undercurrent and leaves a considerably stronger odour impression. The odour of the racemic mixture of **3** and **4** is almost indistinguishable from that of enantiomer **4** and yet milder, more balanced

and hence more pleasant than either of the pure enantiomers. The odour of the natural rose oxide **2**, however, is about five times more intense than that of its oxa-analogue **4**.

The diastereoisomeric acetals of citral and of (*R*)- and (*S*)-citronellal with the enantiomeric butane-1,3-diols, compounds **5** to **12**, exhibit a basically rose-type odour, albeit each with differing intensity and tonality. While there is some evidence of olfactory similarity between compounds of different oxidation states it is apparent that the odours of the dihydro compounds **9** to **12** are more rose-like, more intense and more pleasant than those of the dehydro compounds **5** to **8**. There is thus some ground in ascribing at least a qualitative analogy between the dihydroacetals **9** to **12** on the one hand, and the 'sesqui'-rose oxides [18], even though the latter are more intense, more thoroughbred and show a richer diversity of nuances. The contrast between the 'sesqui'-rose oxides and the citral acetals **5** to **8** is even more pronounced.

Each of the four sesquiterpenoid acetals **9** to **12** has a distinctive olfactory character. The all-*cis* compound **9** exhibits a flowery-green rose-type fragrance similar to that of its diastereoisomer **10** but of greater intensity. Compound **12** differs from its enantiomer **10** in a lower intensity coupled with a fruity undertone. On the other hand the odour of compound **11** is more intense than that of its enantiomer **9** and exhibits a pronounced fatty-aldehydic background.

A striking characteristic of the group of citral acetals **5** to **8** is that the olfactory differences between enantiomers are much greater than between diastereoisomers of the same optical sign. Compounds **8** and **7** exhibit a flowery-spicy scent though it is less marked and less characteristic in the latter. Both **5** and **6** possess a heavy flowery fragrance: in **5** its emphasis is more on a fruity verbena-like note, whereas in **6** a rose-type tonality predominates. The overall odour intensity is incomparably higher in the (–)-compounds **5** and **6** than in the (+)-isomers **7** and **8**.

Experimental Part

(with the valued collaboration of *B. Kuenzi*)

General. – Preparative gas chromatographic separations were performed using a *Wilkens* A 700 Autoprep instrument (10% *Carbowax* 20 M on *Chromosorb* W 95, 2.5 m × 4 mm glass columns) or a *Hupe-Busch* APG 402 instrument (25% *Carbowax* on *Chromosorb* W 40–80, 2 m × 40 mm metal columns), working temperature 150 to 210°. All other analytical methods and instrumentation are as detailed in the preceding paper [18].

(+)- and (–)-Butane-1,3-diols were obtained from the racemate by resolution using camphanoyl chloride as described in [16]. (+)-(*S*)-Butane-1,3-diol showed: $[\alpha]_D^{20} = +27.9°$ ($c = 10$, MeOH) [lit. [19]: $[\alpha]_D^{23} = +25.6°$ ($c = 5$, EtOH)]; (–)-(*R*)-butane-1,3-diol showed: $[\alpha]_D^{20} = -29.4°$ ($c = 10$, MeOH) [lit. [20]: $[\alpha]_D^{25} = -18.8°$ ($c = 4$, EtOH)]. (+)-(*R*)-Citronellal, of $[\alpha]_D^{20} = +10.4°$ ($c = 10$, EtOH), was obtained from commercial *Java Citronella* oil; (–)-(*S*)-citronellal, of $[\alpha]_D^{20} = -14°$ ($c = 10$, EtOH), was obtained from (–)-citronellol [21], of $[\alpha]_D^{20} = +4.1°$ ($c = 10$, EtOH), by oxidation with pyridinium dichromate [22].

Preparation of acetals **3** *to* **12**. – 1. *4-Methyl-2-2'-methylprop-1'-enyl-1,3-dioxane* (**3**+**4**). The following procedure is indicative of that used for the preparation of the other acetals. To a vigorously stirred mixture of (±)-butane-1,3-diol (1.8 g, 0.02 mol), 3-methylbut-2-enal (2 g, 0.025 mol) and calcium carbonate (dry, 10 g) in THF (anhydrous, 100 ml) at –60° under argon was added BF_3-etherate (0.4 ml) [17]. After 30 min the mixture was warmed to 0° and kept at this temperature for 14.5 h, after which saturated $NaHCO_3$-solution (4 ml) was added and the mixture worked up in the usual manner. From the mixture of (±)-*cis*- and -*trans*-oxa-rose oxides thus obtained (2.7 g, 87%, ratio 98.8:1.2) the *cis*-isomer **3**+**4** was isolated pure by preparative GC., b.p. 31°/0.1 Torr; $d_4^{20} = 0.9358$; $n_D^{20} = 1.4515$.

In the same manner there were obtained, from (+)-butane-1,3-diol (+)-(2*R*,4*S*)-4-methyl-2-2'-methylprop-1'-enyl-1,3-dioxane (**3**) ($[\alpha]_D^{20} = +32.5°$; $c = 10$, MeOH), and from (–)-butane-1,3-diol (–)-(2*S*,4*R*)-4-methyl-2-2'-methylprop-1'-enyl-1,3-dioxane (**4**) ($[\alpha]_D^{20} = -34.9°$; $c = 10$, MeOH). There was no change in [α] after reaction times of 7 or 17 h. Likewise, repeated GC. treatment of **3** or **4** caused no racemization.

Spectral data of **3** *and* **4**. – IR. (film): 1440, 1370, 1160, 1130, 1100, 1060, 1018, 988, 960, 948. – ^{1}H-NMR. (CCl_4): 1.16 (*d*, J=6, H_3C–C(4)); 1.66 (*s*, H_3C–C(2′)); 1.71 (br. *s*, H_3C–C(2′)); 1.2–1.55 (*m*, $H_2C(5)$); 3.4–4.2 (*m*, H–C(4) and $H_2C(6)$); 4.93 (*d*, J=7, H–C(2)); 5.11 (*d* with fine splitting, J=7, H–C(1′)). – MS.: 156 (10, M^+), 155 (10), 141 (77), 101 (20), 85 (52), 84 (43), 83 (79), 69 (31), 59 (36), 56 (73), 55 (100), 43 (37), 41 (57), 39 (32), 29 (37), 27 (33).

2. *(–)-(2S,4R,E)-2-2′,6′-Dimethylhepta-1′,5′-dienyl-4-methyl-1,3-dioxane* (**5**) *and (–)-(2S,4R,Z)-2-2′,6′-dimethylhepta-1′,5′-dienyl-4-methyl-1,3-dioxane* (**6**). Each enantiomeric butane-1,3-diol (1.8 g, 0.02 mol) was separately caused to react as described above with citral (geranial/neral mixture, ratio 65:35, 3.8 g, 0.025 mol). With the (–)-enantiomer there was obtained 4.1 g of a mixture of **5** and **6**, which were separated by GC.

Acetal **5** had $[\alpha]_D^{20} = -17°$ (c = 10, EtOH); *acetal* **6** had $[\alpha]_D^{20} = -36.6°$ (c = 7, EtOH). – ^{1}H-NMR., see *Figure 1;* MS., see *Table 1.*

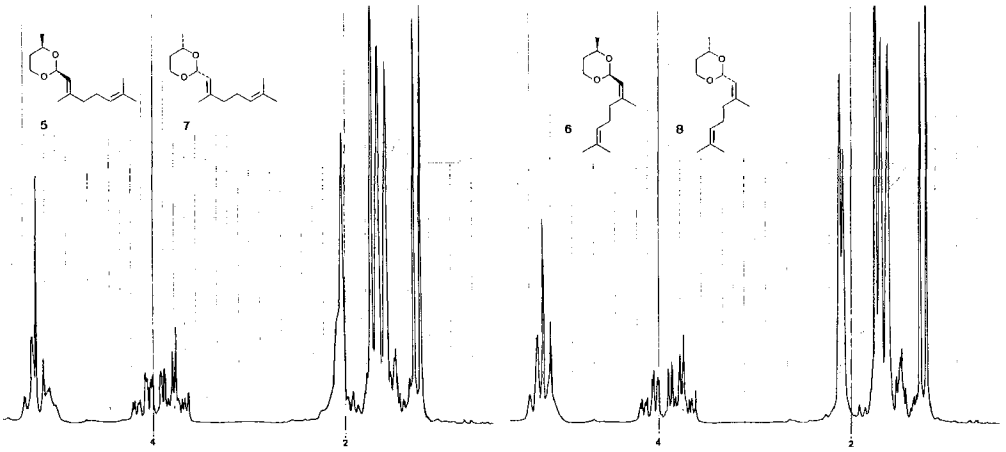

Fig. 1. *^{1}H-NMR. signals* (90 MHz, $CDCl_3$) *of compounds* **5** *to* **8**

Table 1. *Mass spectra of compounds* **5** *to* **8**

Compound	224 (M^+)	223	209	181	155	134	123	109	101	84	69	55	41
5	6	3	2	8	18	10	8	15	39	30	80	100	68
6	9	2	4	5	10	12	11	34	27	38	76	100	75
7	8	2	3	6	11	12	11	32	25	36	73	100	79
8	4	2	1	5	15	9	7	12	35	31	74	100	59

The assignment of double bond geometry in **5** and **6** is based on their ^{13}C-NMR. spectra (see *Fig. 2*), as compared with those of geraniol and nerol [23].

From (+)-butane-1,3-diol there were obtained *acetals* **7** ($[\alpha]_D^{20} = +18.4°$; c = 3.9, EtOH) and **8** ($[\alpha]_D^{20} = +34.2°$; c = 3, EtOH). – ^{1}H-NMR., see *Figure 1;* MS., see *Table 1.*

3. *Diastereoisomeric acetals from citronellal,* **9** *to* **12**. In each case, the yield was *ca.* 90%. From (–)-butane-1,3-diol and (+)-citronellal there was obtained *(–)-(2S,4R,2′R)-2-2′,6′-dimethylhept-5′-enyl-4-methyl-1,3-dioxane* (**9**), $[\alpha]_D^{20} = -1.8°$ (c = 10.6, EtOH). From (–)-butane-1,3-diol and (–)-

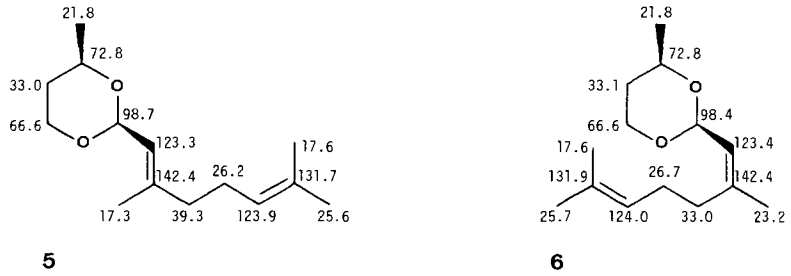

Fig. 2. *^{13}C-NMR. chemical shifts of compounds* **5** *and* **6**

citronellal there was obtained *(−)-(2*S*,4*R*,2'*S*)-2-2',6'-dimethylhept-5'-enyl-4-methyl-1,3-dioxane* (**10**), $[\alpha]_D^{20} = -5.2°$ ($c = 9.4$, EtOH). From (+)-butane-1,3-diol and (−)-citronellal there was obtained *(+)-(2*R*,4*S*,2'*S*)-2-2',6'-dimethylhept-5'-enyl-4-methyl-1,3-dioxane* (**11**), $[\alpha]_D^{20} = +2°$ ($c = 10.2$, EtOH). From (+)-butane-1,3-diol and (+)-citronellal there was obtained *(+)-(2*R*,4*S*,2'*R*)-2-2',6'-dimethylhept-5'-enyl-4-methyl-1,3-dioxane* (**12**), $[\alpha]_D^{20} = +5°$ ($c = 10$, EtOH). – ^{1}H-NMR., see *Figure 3;* MS., see *Table 2.*

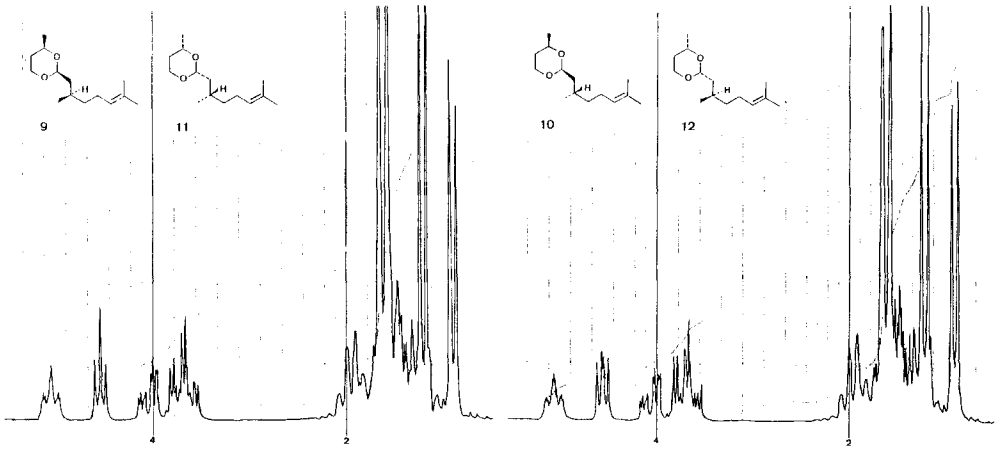

Fig. 3. *^{1}H-NMR. signals* (90 MHz, $CDCl_3$) *of compounds* **9** *to* **12**

Table 2. *Mass spectra of compounds* **9** *to* **12**

Compound	226 (M^+)	225	211	136	121	109	101	89	69	55	41
9	3	6	1	22	70	28	44	32	45	100	56
10	2	5	1	20	66	26	42	29	44	100	53
11	3	6	1	21	69	29	44	31	46	100	60
12	2	5	1	19	64	25	41	30	44	100	54

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